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(54) Title: NOVEL 2-OXO-HETEROCYCLIC COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

(57) Abstract: The present invention is related to new 2-oxo-cyclic compound the process for preparing them and a pharmaceutical composition comprising the same. The present invention provides a pharmaceutical composition for preventing and treating the inflammatory disease comprising the pain or inflammation caused by rheumatic disease, for example, rheumatoid arthritis, spondyloarthopathies, gout, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, and inflammatory syndrome for example, from myositis, gingivitis, synovitis, ankylosing spondylitis, burstitis, burns and scar, inflammatory Crohn's disease, Types I diabetes. therefore, it can be used as the therapeutics for treating and preventing inflammatory diseases.

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NOVEL 2-OXO-HETEROCYCLIC COMPOUNDS AND THE PHARMACEUTICAL COMPOSITIONS COMPRISING THE SAME

Technical Field

The present invention relates to novel 2-oxo-heterocyclic compounds as a potent anti-inflammatory agent and the pharmaceutical compositions comprising the same.

Background Art

The inflammation caused by mechanical scars or various infection of bacteria *et al* is a normal response of human body associated with an edema, a pain *etc.* Generally, the syndrome of arthritic inflammation occurs temporally, however, it causes to long-term and eventual deformity if it is progressed to be severe. The arthritic disease can be classified into several diseases according to the respective disease such as rheumatoid arthritis (RA), rheumatic inflammation related disease *etc.* Among them, in particular, arthritic inflammation is the most frequently occurred and chronic disease characterized in the inflammatory change at the synovial membrane of the inner layer of articular capsule, which may progress to effect on all the joints of human body and become worse to be a disabled person. A progressive arthritic disease such as rheumatic arthritis gives rise to joint obstacle such as a joint aberrance and acampsia, which often results in severe physical disorder caused by the absence of effective treatment and continuous aggravation of the disease.

It has been known that osteoarthritis (OA) correlates with complex and multi-factors, however, most important factor among them is the inflammation of synovial fluid. The injury of synovial fluid may promotes the dissociation of proteoglycan (PG) as a result of the interaction between synovial cells and cartilage cells. The activated synovial cells reproduce numerous factors which may induce the loss of articular cartilage, for example, interleukin-1, tumor necrosis factor (TNF-alpha) and prostaglandins. The direct injury of cartilage cells further accelerates the reproduction of matrix metalloprotease (MMP) activating enzymes such as collagenase, stromelysin and gelatinase and various inflammatory mediators. Wherever the function of joint cartilage reduces, it gives rise to occurring OA diseases. The decrease of PGs at OA joint tissue reduces the resilence of cartilage, which endows cartilage cell, subcartilaginous osteocyte and synovial cell with a mechanical stress.

Both of OA and rheumatic arthritis (RA) are representative diseases destructing joint cartilage and being characterized in topical erosion of cartilage surface. For example, it has been reported that the introduction of radio-labeled sulfuric acid salt into

the femoral joint cartilage of OA patients is significantly decreased compared with that of control group, which indicates that the dissociating rate of cartilage in OA patient is increased (Mankin et al., *J. Bone Joint Surg.*, **52A**, pp424-434, 1970).

Four types of proteinase, i.e., serine, cystein, aspartic acid and metalloprotease exist in mammalian cell. The metalloprotease, one of the proteinase, has been reported to be an important factor for the extra-cellular substrate hydrolyzing action of joint cartilage in OA and RA patients and further the increased activity of collagenase and stromelysin has been found in the cartilage of OA patient, of which activity is closely interrelated with the severity of OA or RA disease (Mankin et al., *Arthritis Rheum.*, **21**, pp761-766, (1978); Woessner et al., *Arthritis Rheum.*, **26**, pp63-68, (1983) and *Ibid.*, **27**, pp305-312, (1984)). Agrekanase has been also found in OA and RA patient recently and it shows metalloprotease enzyme similar activity and provides with the specific fragmented product of proteoglycans (Lohmander L. S. et al., *Arthrits Rheum.*, **36**, pp1214-1222, 1993),

TNF (Tumor Necrosis Factor), a cytokine bound to cells, is processed from 36kD precursor type to 17kD activated or thereof. It has been found that TNF is a first controlling factor of acute phase response similar to the phenomenon occurred during inflammation, fever, acute infection and shock in human and animal, therefore the excess reproduction of TNF could be a cause of death. At present, it has been reported that the prevention of TNF reproduction could treat various diseases together with autoimmune disease such as rheumatoid arthritis (RA), insulin-independent diabetes and Crohn's disease (Lohmander L. S. et al., *Arthritis Rheum.*, **36**, pp1214-1222, 1993; Macdonald T. et al., *Clin. Exp. Immunol.*, **81**, p301, 1990).

Accordingly, the reproduction inhibitors of TNF have potentially therapeutic importance in the treatment of inflammatory diseases. Recently, matrix metalloprotease as well as other metalloproteases known to be as TNF-C (Tumor Necrosis Factor-Convertase, can be transformed from inactivated form thereof into activated form thereof (Gearing et al., *Nature*, **370**, p555 1994), therefore the inhibiting either the transformation of MPs or the release of activated TNF-alpha from the cell thereby may be an important mechanism in the treatment of inflammatory diseases.

Since the overproduction of TNF is a distinguished phenomenon in lots of diseases having characteristic of the tissue lysis mediated by MMP, the inhibitor of both MMP and TNF has favorable advantage in the treatment of specific inflammatory diseases correlated with both mechanism.

PCT WO 92/213260 A1 discloses N-carboxyalkylpeptidyl compounds useful as an enzyme inhibitor of hydroxamates and carboxylates matrix MMP; PCT WO 90/05716 A1 and PCT WO 92/13831 A1 disclose an hydroxamate matrix collagenase

inhibitor; PCT WO 94/2446 A1 discloses natural amino acid derivatives useful as an MMP inhibitor; PCT WO 95/9841 A1 discloses hydroxamate derivatives useful as a cytokine inhibitor; GB A 2,268, 934 and PCT WO 94/24140 A1 disclose a hydroxamate inhibitor of MMP inhibiting TNF reproduction, the disclosure of which cited documents are incorporated herein by reference.

To treat RA or OA disease, conventional drugs for example, steroids such as cortisone and other ACTH (adrenocorticotrophic hormone); NSAID (Non-steroidal anti-inflammatory drug) such as aspirin, piroxicam, indomethacin *etc*; gold agents such as aurothioglucose, gold sodium thiomalate an auranofin *etc*; anti-rheumatic drug such as chloroquinone, D-penicillamine *etc*; gout inhibitors such as colchicines; and immuno-suppressing agents such as cyclophosphamide, azathioprine, methotrexate, levamisole etc have been prescribed till now. However, the treatment with conventional drugs has not provided with satisfactory efficacy and has various adverse effects, which limits the usage of conventional drugs.

For example, anti-inflammatory drugs such as asprin or butazolin have been used to alleviate the syndrome of OA and RAs, however, the consistent administration of the drugs is difficult because of their adverse effects, for example, *i.e.*, severe stomach irritation resulting in gastritis, stomach ulcer *etc*.

Accordingly, there have been studied and investigated to develop new satisfactory anti-rheumatic agents which can solve the problems of conventional drugs, in particular, which can improve anti-inflammatory efficacy and provide with safe long-term administration without adverse action till now.

Present inventors extensively investigated to find new compounds showing strong inhibiting activity for the reproduction of NO and TNF-alpha, finally found new 2-oxo-heterocyclic compounds showing potent inhibition effects on the reproduction of NO and TNF-alpha, and completed present invention.

SUMMARY OF THE INVENTION

The present invention provides a novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof showing strong inhibiting activity for the reproduction of NO and TNF-alpha .

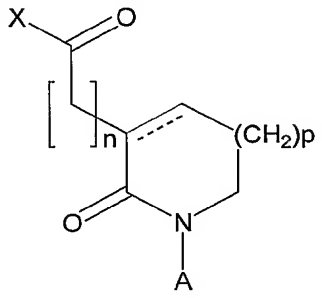
The present invention also provides a pharmaceutical composition comprising a novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof

as an active ingredient in an effective amount to treat and prevent inflammation diseases.

The present invention also provides a use of novel 2-oxo-heterocyclic compound and the pharmacologically acceptable salt thereof for the preparation of pharmaceutical composition to treat and prevent inflammatory diseases.

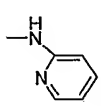
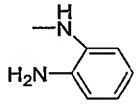
Disclosure of the invention

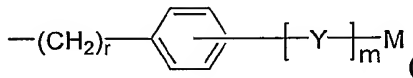
Thus, the present invention provides a novel compound represented by the following general formula (I), and the pharmaceutically acceptable salt:



(I)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

A is an hydrogen, A1 group or  (A2),

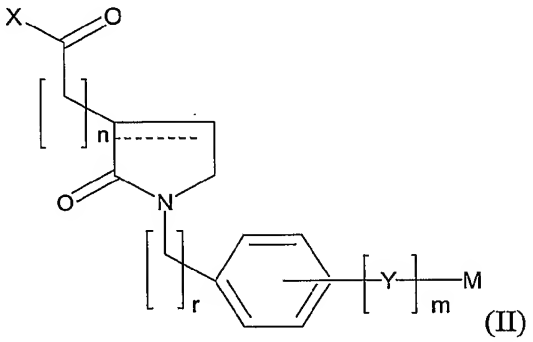
A1 is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group, wherein Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group, M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group, m and r is independently an integer of 1 to 5 respectively in A2 residue;

p is an integer of 0, 1 or 2;

n is an integer of 1 to 5;

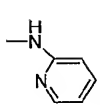
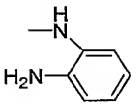
dotted line (═) means single bond or double bond.

In preferred embodiment, the present invention also provides the compounds represented by following general formula (II), the pharmaceutically acceptable salt or the isomer thereof:



(II)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (┅)means single bond or double bond.

The preferred compounds of general formula (II) is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-

propionamide,

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid,

N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide,

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide,

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide,

3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

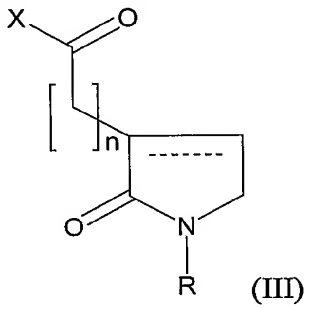
N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-

3-yl]-propionamide,

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

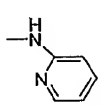
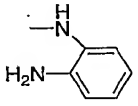
N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

In preferred embodiment, the present invention also provides the compounds represented by following general formula (III), the pharmaceutically acceptable salt or the isomer thereof:



(III)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (┅) means single bond or double bond.

The preferred compounds of general formula (III) is one selected from the group consisting of;

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

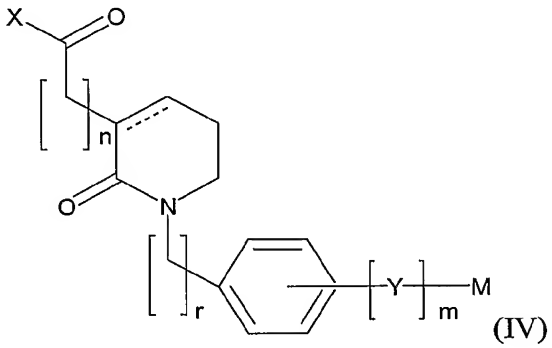
N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

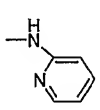
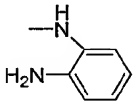
N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

In preferred embodiment, the present invention also provides the compounds represented by following general formula (IV), the pharmaceutically acceptable salt or the isomer thereof:



(IV)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (┅) means single bond or double bond.

The preferred compounds of general formula (IV) is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetragydropyridin-3-yl]-N-hydroxypropionamide,

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide,

N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide,

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic

acid,

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid,

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide,

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid,

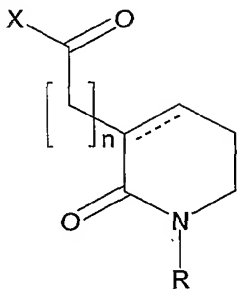
4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide,

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide,

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide,

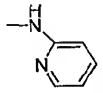
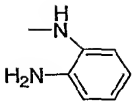
N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide.

In preferred embodiment, the present invention also provides the compounds represented by following general formula (V), the pharmaceutically acceptable salt or the isomer thereof:



(V)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group, preferably, the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (┈) means single bond or double bond.

The preferred compounds of general formula (V) is one selected from the group consisting of;

3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-[1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide.

It is another object of the present invention to provide the pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (V) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to alleviate or treat pain diseases or inflammatory diseases together with pharmaceutically acceptable carriers or diluents.

The inventive compounds represented by general formula (I) to (V) can be

transformed into their pharmaceutically acceptable salt and solvates by the conventional method well known in the art. For the salts, acid-addition salt thereof formed by a pharmaceutically acceptable free acid thereof is useful and can be prepared by the conventional method. For example, after dissolving the compound in the excess amount of acid solution, the salts are precipitated by the water-miscible organic solvent such as methanol, ethanol, acetone or acetonitrile to prepare acid addition salt thereof and further the mixture of equivalent amount of compound and diluted acid with water or alcohol such as glycol monomethylether, can be heated and subsequently dried by evaporation or filtrated under reduced pressure to obtain dried salt form thereof.

As a free acid of above-described method, organic acid or inorganic acid can be used. For example, organic acid such as methansulfonic acid, *p*-toluensulfonic acid, acetic acid, trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonylic acid, vanillic acid, hydroiodic acid and the like, and inorganic acid such as hydrochloric acid, phosphoric acid, sulfuric acid, nitric acid, tartaric acid and the like can be used herein.

Further, the pharmaceutically acceptable metal salt form of inventive compounds may be prepared by using base. The alkali metal or alkali-earth metal salt thereof can be prepared by the conventional method, for example, after dissolving the compound in the excess amount of alkali metal hydroxide or alkali-earth metal hydroxide solution, the insoluble salts are filtered and remaining filtrate is subjected to evaporation and drying to obtain the metal salt thereof. As a metal salt of the present invention, sodium, potassium or calcium salt are pharmaceutically suitable and the corresponding silver salt can be prepared by reacting alkali metal salt or alkali-earth metal salt with suitable silver salt such as silver nitrate.

The pharmaceutically acceptable salt of the compound represented by general formula (I) to (V) comprise all the acidic or basic salt, which may be presented at the compounds, if it does not indicated specifically herein. For example, the pharmaceutically acceptable salt of the present invention comprise the salt of hydroxyl group such as the sodium, calcium and potassium salt thereof; the salt of amino group such as the hydrogen bromide salt, sulfuric acid salt, hydrogen sulfuric acid salt, phosphate salt, hydrogen phosphate salt, dihydrophosphate salt, acetate salt, succinate salt, citrate salt, tartarate salt, lactate salt, mandelate salt, methanesulfonate(mesylate) salt and *p*-toluenesulfonate (tosylate) salt etc, which can be prepared by the

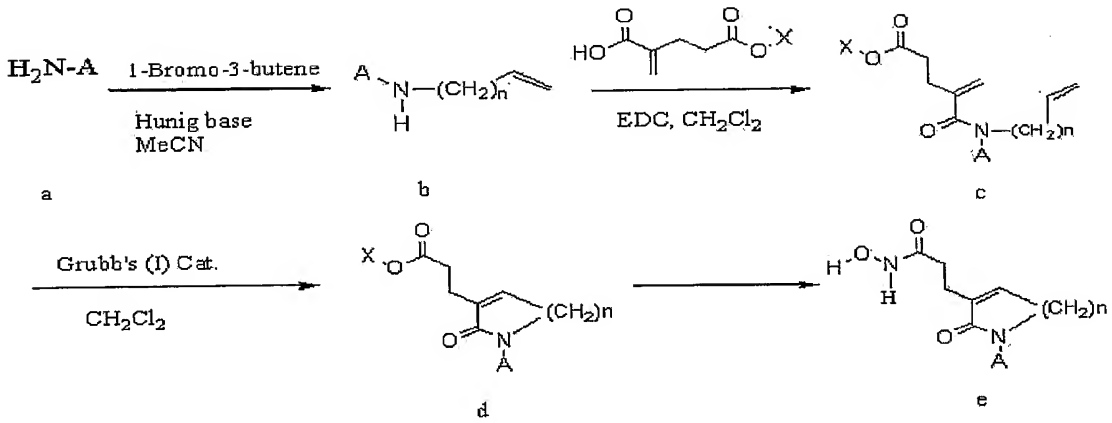
conventional method well known in the art.

There may exist in the form of optically different diastereomers since the compounds represented by general formula (I) to (V) have unsymmetrical centers, accordingly, the compounds of the present invention comprise all the optically active isomers, R or S stereoisomers and the mixtures thereof. Present invention also comprises all the uses of racemic mixture, more than one optically active isomer or the mixtures thereof as well as all the preparation or isolation method of the diastereomer well known in the art.

The compounds of the invention of formula (I) to (V) may be chemically synthesized by the methods explained by following reaction schemes hereinafter, which are merely exemplary and in no way limit the invention. The reaction schemes show the steps for preparing the representative compounds of the present invention, and other compounds also may be produced by the following steps with appropriate modifications of reagents and starting materials, which are envisaged by those skilled in the art.

GENERAL SYNTHETIC PROCEDURES

Scheme 1



As depicted in above Scheme **1**, the scheme explains the process for preparing hydroxamic acid compound (**e**) consisting of 4 steps;

At the 1st step, compound (**a**) is reacted with 1-bromo-3-butene under organic solvent in the presence of Hunig base to synthesize compound (**b**). In this step, an organic solvent such as acetonitrile, dichloromethane *etc* is preferable and diethylisopropylamine can be used as a Hunig base in the amount of 2 to 3 equivalents to the compound (**a**). It is preferable the reaction is performed at the temperature ranging from 0℃ to room temperature (RT).

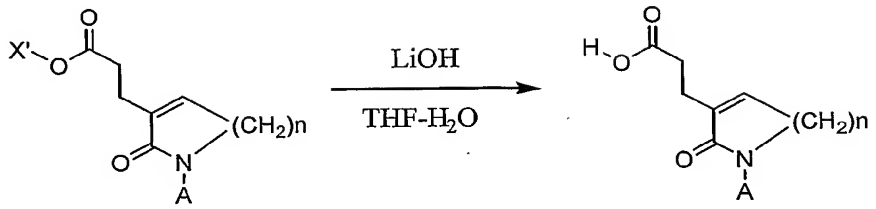
At the 2nd step, the compound (**b**) obtained in step 1 is reacted with mono acid in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide(EDC) under an organic solvent to synthesize the compound (**c**). In this step, an organic solvent such as dichloromethane, THF *etc* are preferable and the mono acid such as 2-methylene-pentandionic acis-5-methyl ester in the amount of 1 to 1.2 equivalents to the compound (**b**) is preferable. It is preferable the reaction is performed at the temperature ranging from 0℃ to RT.

At the 3rd step, the compound (**c**) obtained in step 2 is converted into the compound (**d**) in the presence of Grubb's (I) catalyst such as Ruthenium catalyst under organic solvent. In this step, it is preferable to use the catalyst in the amount of 0.02 to 0.1 equivalents to the compound (**c**) at the temperature ranging from 0℃ to RT.

At the 4th step, the compound (**d**) obtained in step 3 is reacted with amine salt to synthesize hydroxamic acid compound (**e**) in case that X is NHOH in general formula I compounds. In this step, it is preferable to use potassium hydroxamide ($KONH_2$) in the amount of 2 to 3 equivalents to the compound (**d**) at the temperature ranging from

0℃ to RT.

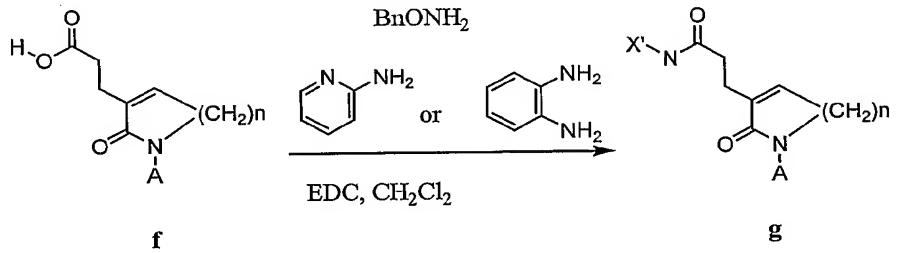
Scheme 2



d **f**

As depicted in the above Scheme 2, the ester compounds (**d**) is reacted with hydroxide metal salt under the organic solvent such as THF to synthesize the carboxylic acid (**f**). In the reaction, it is preferable to use LiOH in the amount of 2 to 3 equivalents to the compound (**d**) at the temperature ranging from 0℃ to RT.

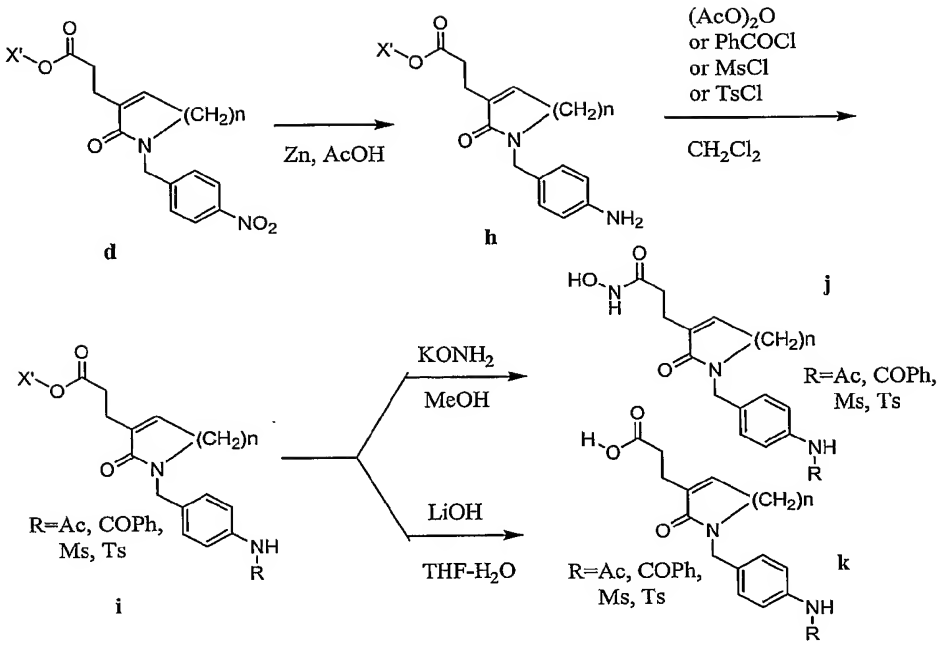
Scheme 3



f **g**

As depicted in the above Scheme 3, the carboxylic acid compound (**f**) obtained in Scheme 2 is reacted with benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) under organic solvent to synthesize the amide compounds of which X is benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene group. In the reaction, it is preferable to use benzyloxyamine($BnONH_2$), pyridylamine or diaminobenzene in the amount of 1 to 1.5 equivalents to the compound (**f**) at the temperature ranging from 0℃ to RT.

Scheme 4



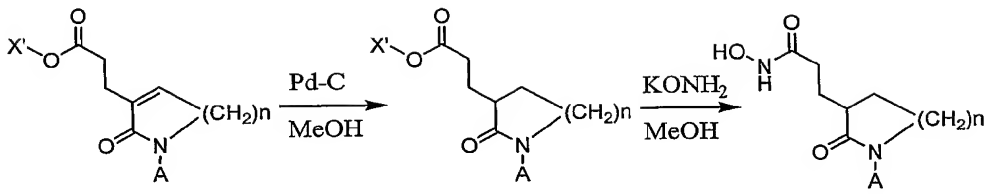
As shown in the above Scheme 4, the hydroxamide compound (**j**) and carboxylic acid compound (**k**) are prepared by following procedure from the ester compounds (**d**):

At the 1st step, the compound (**d**) prepared from Scheme 2 is reacted with zinc dust under organic solvent to synthesize the compound (**h**). In this step, it is preferable to use the zinc in the amount of 2 to 5 equivalents of the compound (**h**).

At the 2nd step, the compound (**h**) obtained in step 1 is reacted with $(AcO)_2O$, PhCOCl, MsCl or TsCl to synthesize the compound (**i**). In the reaction, it is preferable to use $(AcO)_2O$, PhCOCl, MsCl or TsCl in the amount of 1 to 3 equivalents to the compound (**h**).

At the 3rd step, the compound (**i**) obtained in step 2 is reacted with amine salt under the organic solvent such as methanol to produce the hydroxamide compound (**j**), *i.e.*, the general formula I compound wherein X is NHOH where the amine salt is preferably used in the amount of 2 to 3 equivalents to the compound (**i**), or with hydroxide metal salt such as LiOH under the organic solvent such as THF to produce the carboxylic acid compound (**k**), *i.e.*, the general formula I compound wherein X is OH where the metal salt is preferably used in the amount of 2 to 3 equivalents to the compound (**i**).

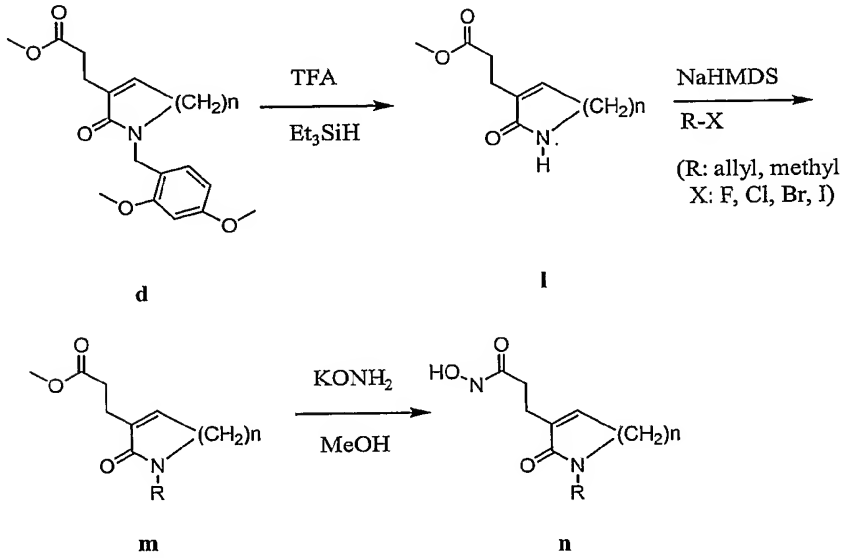
Scheme 5



d **l** **m**

As shown in Scheme 5, the 1,2,5,6-dihydropyridine compound (**d**) is reduced to the piperidine compound (**l**) by reacting with palladium-carbon (Pd/C) under alcohol solvent in the amount of 0.1 to 0.2 equivalents of compound (**d**) and furthermore the piperidine compound (**l**) is reacted with $KONH_2$ in MeOH to synthesize the compound (**m**). In the reaction, it is preferable to use the amine salt in the amount of 2 to 3 equivalents to the compound (**m**) at the temperature ranging from 0℃ to RT.

Scheme 6

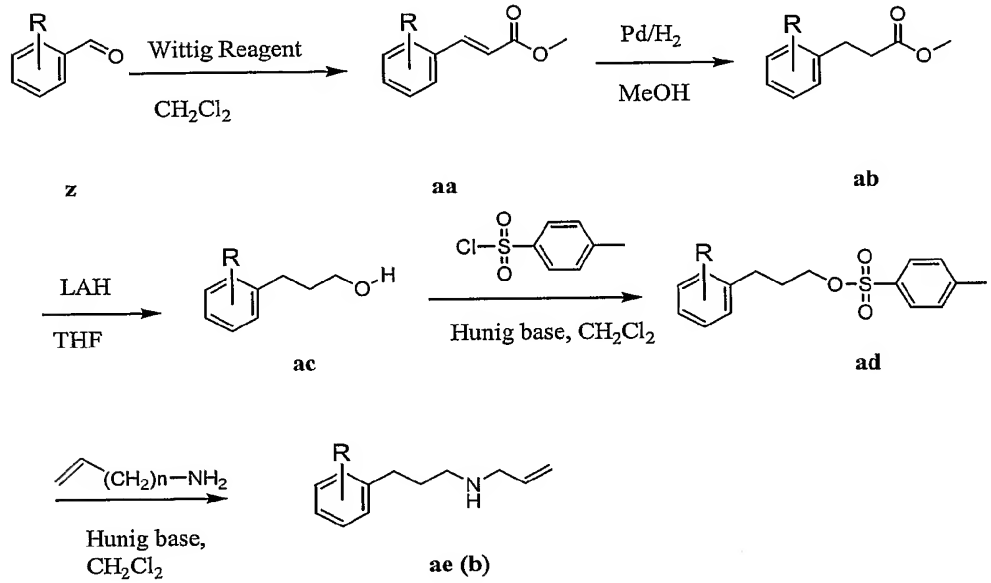


d **l**

m **n**

As shown in Scheme 6, the benzyl compound **(d)** is reacted with trifluoroacetic acid(TFA) in the presence of the amount of 1 to 1.5 equivalent of the compound (d) to produce the compound **(l)**. The compound **(l)** is further reacted with hexamethyldisilylazide sodium (NaHMDS) in THF solvent and subsequently reacted with R-X (R: ally, methyl *etc*, X: halogen atom) to produce the compound **(m)**. In this reaction, it is preferable to use the NaHMDS in the amount of 1 to 1.5 equivalents to the compound (l).

Scheme 7



As shown in Scheme 7, the compound **(b)** as a starting material is prepared by following procedure: At the 1st step, the compound **(z)** which can be procure by conventional market or chemical company is reacted with Wittig reagent under the organic solvent such as dichloromethane to synthesize to the compound **(aa)**. In this step, it is preferable to use the Wittig reagent in the amount of 1.5 to 2 equivalents of the compound **(z)** at the temperature ranging from 60 to 70℃.

At the 2nd step, the compound **(aa)** obtained in step 1 is reacted with Pd/C under H_2 atmosphere in the amount of 0.1 to 0.2 equivalents of the compound **(aa)** under ethyl alcohol solvent to synthesize the compound **(ab)**.

At the 3rd step, the compound **(ab)** obtained in step 2 is reacted with lithium aluminum hydride (LAH) under the organic solvent such as THF to produce the

compound **(ac)** at 0 ℃.

At the 4th step, the compound **(ac)** is subsequently reacted with p-toluenesulfonylchloride in the presence of diisopropylethylamine or 4-(dimethylamino) pyridine in the amount of 0.1 to 0.2 equivalents of the compound **(aa)** under ethyl alcohol solvent to synthesize the compound **(ab)**.

At the 5th step, both of allyl amine and Hunig base (diisopropylethylamine) are added to the compound **(ad)** dissolved in acetonitrile, mixed and stirred for six hours at 80 ℃ to produce the compound **(ae)**, one of the compound **(b)**.

The present invention also provides a pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (V) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent inflammatory diseases together with pharmaceutically acceptable carriers or.

The compound of formula (I) to (V) according to the present invention can be provided as a pharmaceutical composition containing pharmaceutically acceptable carriers, adjuvants or diluents. For example, the compounds of the present invention can be dissolved in oils, propylene glycol or other solvents, which are commonly used to produce an injection. Suitable examples of the carriers include physiological saline, polyethylene glycol, ethanol, vegetable oils, isopropyl myristate, etc., but are not limited to them. For topical administration, the compounds of the present invention can be formulated in the form of ointments and creams.

The pharmaceutical compositions comprising the compound of the present invention can be treat and prevent the inflammatory disease comprising the pain or inflammation caused by rheumatic disease, for example, rheumatoid arthritis, spondyloarthopathies, gout, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, and inflammatory syndrome for example, from myositis, gingivitis, synovitis, ankylosing spondylitis, burstitis, burns and scar, inflammatory Crohn's disease, Types I diabetes.

The compound of the present invention has potent anti-inflammatory activity, and the pharmaceutical composition of the present invention thus may be employed to treat or prevent the inflammatory disease comprising the pain or inflammation caused by rheumatic disease and inflammatory syndrome.

The present invention also provides a method of preventing or treating the inflammatory disease comprising the pain or inflammation caused by rheumatic disease and inflammatory syndrome which comprises administering compound selected from the group consisting of compounds of formula (I) to (V) or pharmaceutical acceptable salts thereof in need of such prevention or treatment a therapeutically effective amount of the salt or a pharmaceutically acceptable hydrate thereof as an anti-inflammatory agent.

The present invention also provides a use of the compounds as an active ingredient in medicines for treating or preventing the inflammatory disease comprising the pain or inflammation caused by rheumatic disease and inflammatory syndrome.

Hereinafter, the following formulation methods and excipients are merely exemplary and in no way limit the invention.

The compounds of the present invention in pharmaceutical dosage forms may be used in the form of their pharmaceutically acceptable salts, and also may be used alone or in appropriate association, as well as in combination with other pharmaceutically active compounds.

The compounds of the present invention may be formulated into preparations for injections by dissolving, suspending, or emulsifying them in aqueous solvents such as normal saline, 5% Dextrose, or non-aqueous solvent such as vegetable oil, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol. The formulation may include conventional additives such as solubilizers, isotonic agents, suspending agents, emulsifying agents, stabilizers and preservatives.

The desirable dose of the inventive compounds varies depending on the condition and the weight of the subject, severity, drug form, route and period of administration, and may be chosen by those skilled in the art. However, in order to obtain desirable effects, it is generally recommended to administer at the amount ranging 0.0001 - 100 mg/kg, preferably 0.001 – 100 mg/kg by weight/day of the inventive compounds of the present invention. The dose may be administered in single or divided into several times per day. In terms of composition, the compounds should be present between 0.0001 to

10% by weight, preferably 0.0001 to 1% by weight based on the total weight of the composition.

The pharmaceutical composition of present invention can be administered to a subject animal such as mammals (rat, mouse, domestic animals or human) via various routes. All modes of administration are contemplated, for example, administration can be made orally, rectally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebroventricular injection.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

BEST MODE FOR CARRING OUT THE INVENTION

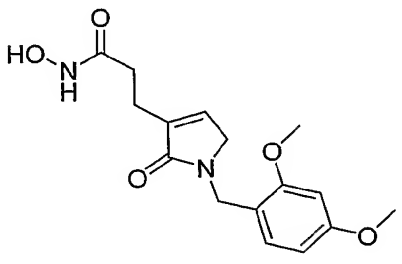
It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, use and preparations of the present invention without departing from the spirit or scope of the invention.

The present invention is more specifically explained by the following examples. However, it should be understood that the present invention is not limited to these examples in any manner.

EXAMPLES

The following Reference Example, Examples and Experimental Examples are intended to further illustrate the present invention without limiting its scope.

Example 1. Preparation of 3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide(1e)



Step 1. Preparation of allyl-(2,4-dimethoxybenzyl)amine (1b)

0.32 ml of allylbromide (3.66 mmol) and 0.7 ml of diisopropyl ethylamine (3.99 mmol) were added to the reaction solution containing 500 mg of 2, 4-dimethoxybenzylamine (3.33 mmol) dissolved in methylene chloride with stirring and the solution was left alone at room temperature. After the reaction mixture was neutralized with 10% NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 276 mg of allyl-(2,4-dimethoxybenzyl)amine (1b) (yield : 40%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J*= 8.1 Hz, 1H), 6.44-6.39 (m, 2H), 5.99-5.86 (m, 1H), 5.21-5.09 (m, 2H), 3.79 (d, *J*= 6.0 Hz, 6H), 3.74 (s, 2H), 3.23 (d, *J*= 6.0 Hz, 2H)

Step 2. Preparation of 4-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (1c)

253 mg of 2-methylene-pentane dionate-5-methyl ester (1.6 mmol), 331 mg of [3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.73 mmol) and 48 mg of 4-(dimethylamino)pyridine (0.39 mmol) were added to 0.5 M of reaction solution dissolving the compound (1b) prepared by above step 1 in methylene chloride and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with saturated 10 ml of $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 324 mg of 4-[allyl-(2,4-dimethoxy-benzyl)-carbamoyl]-pent-4-enoic acid methyl ester (1c) (yield : 70%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H), 6.44 (d, 2H), 5.72 (s, 1H), 5.12 (s, 4H), 4.56-4.81 (m 2H), 3.91-3.83 (m, 2H), 3.78 (d, *J*= 5.3 Hz, 6H), 3.65 (d, *J*= 1.4 Hz, 3H), 2.63 (t, *J*= 5.7 Hz, 2H), 2.54 (t, *J*= 5.4 Hz, 2H)

Step 3. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (1d)

324 mg of the compound (1c) (0.933 mmol) prepared by the above Step 2 was

added to the catalyst solution containing 74mg of ruthenium (0.09 mmol) dissolved in 93 ml of CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 268 mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrole-3-yl]-propionic acid methyl ester (1d) (yield : 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J*= 9.0 Hz, 1H), 6.61(br t, 1H), 6.43(s, 1H), 6.40 (d, *J*= 2.7 Hz, 1H), 4.56 (s, 2H), 3.78(d, *J*= 5.4 Hz, 9H), 3.65(s, 2H), 2.61(s, 4H)

Step 4. Preparation of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (1e)

100mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.313 mmol) and then 1.7 M methanolic suspension solution containing NH_2OK (0.27 ml, 0.47 mmol) was added thereto at 0° C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 50 mg of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (1e) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.04 (d, *J*= 8.1 Hz,1H), 6.83 (s, 1H), 6.53-6.44 (m, 2H), 4.54(s, 2H), 3.81 (t, *J*= 2.0 Hz, 6H), 2.56 (t, *J*= 7.2 Hz, 2H), 2.34 (t, *J*= 7.4 Hz, 2H), 1.9 (s, 3H)

Example 2. Preparation of 3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (2e)

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (2e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 3. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (3e)

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (3e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 4. Preparation of N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4e)

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 5. Preparation of N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5e)

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 6. Preparation of N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6e)

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 7. Preparation of N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (7e)

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (7e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 8. Preparation of N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8e)

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8e) was prepared by the similar procedure described in above Example 1 (*See* Table 1a).

Example 9. Preparation of N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (9e)

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (9e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

Example 10. Preparation of N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (10e)

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (10e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

Example 11. Preparation of N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (11e)

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (11e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

Example 12. Preparation of 3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (12e)

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (12e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

Example 13. Preparation of 3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (13e)

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (13e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

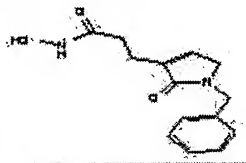
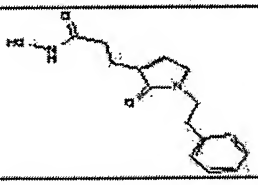
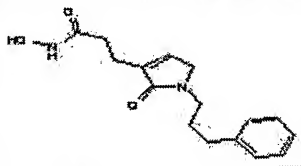
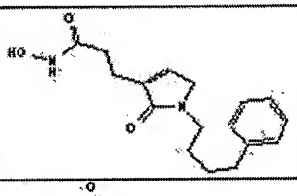
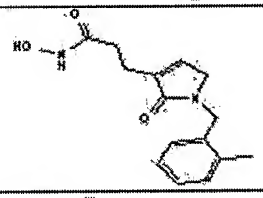
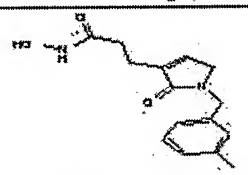
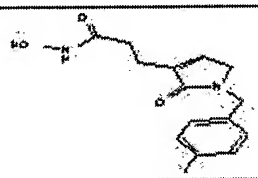
Example 14. Preparation of 3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (14e)

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide (14e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

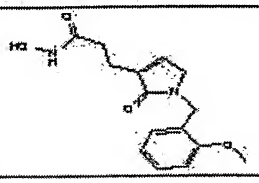
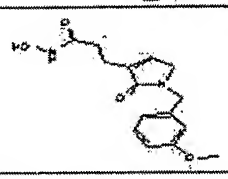
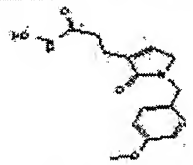
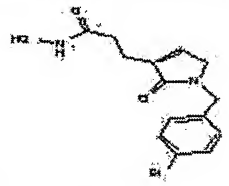
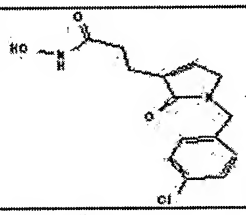
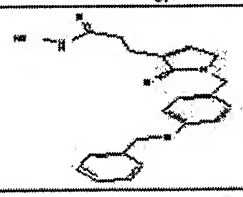
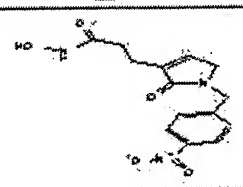
Example 15. Preparation of N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (15e)

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (15e) was prepared by the similar procedure described in above Example 1 (*See* Table 1b).

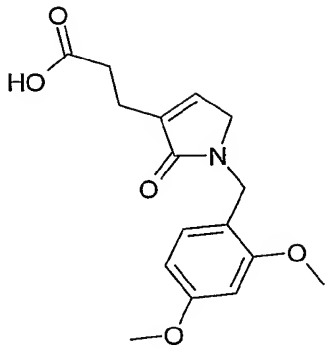
[Table 1a]

Example	Chemical structure	NMR spectrum
2		7.30-7.14 (m, 5H), 6.71 (d, *J*= 18.3 Hz, 1H), 4.59 (d, *J*= 7.8 Hz, 2H), 3.73 (s, 2H), 2.63 (s 4H).
3		7.25-7.09 (m ,5H), 6.64 (s, 1H), 3.62 (t, *J* = 6.1 Hz, 4H), 2.81 (t, *J*= 7.3 Hz, 2H), 2.52 (s, 2H), 2.30 (d, *J*= 6.6 Hz, 2H)
4		7.21 (d, *J*= 7.5 Hz, 2H), 7.12(d, *J*= 6.6 Hz, 3H), 6.72 (s, 1H), 3.75 (s, 2H), 3.41 (s, 2H), 2.57 (d, *J*= 6.3 Hz, 6H), 2.44 (s, 1H), 1.82 (s, 2H)
5		7.28-7.12 (m, 5H), 6.73 (s, 1H), 3.78 (d, *J*= 9.0 Hz, 2H), 3.43 (s, 2H), 2.61 (s, 5H), 1.58 (s, 5H)
6		7.12 (s, 5H), 6.67 (s, 1H), 4.58 (d, *J*= 8.4 Hz, 2H), 3.64 (s, 2H), 2.61 (s, 4H), 2.34-2.22 (m, 3H)
7		7.15 (d, *J*= 6.9 Hz, 1H), 7.02-6.95 (m, 3H), 6.74 (s, 1H), 4.52 (d, *J*= 8.4 Hz, 2H), 3.70 (s, 2H), 2.60 (s, 3H), 2.27 (d, *J*= 4.8 Hz, 4H)
8		7.09-7.03 (m, 4H), 6.70 (d, *J*= 18.3 Hz, 1H), 4.54 (d, *J*= 7.2 Hz, 2H), 3.70 (s, 2H), 2.61 (s, 3H), 2,45 (s, 1H), 2.28 (d, *J*= 13.5 Hz, 3H)

[Table 1b]

Example	Chemical structure	NMR spectrum or LC-MS data
9		7.23-7.18 (m, 1H), 7.08 (d, *J*= 3.5 Hz, 1H), 6.84 (dd, *J*= 5.8 Hz, 2H), 6.72 (s, 1H), 4.59 (s, 2H), 3.78 (s, 3H), 3.75 (s, 2H), 2.60 (s, 2H), 2.44 (s, 2H)
10		7.16 (t, *J*= 4.8 Hz, 1H), 6.73 (t, *J*= 5.4 Hz, 3H), 6.68 (s, 1H), 4.53 (d, *J*= 10.5 Hz, 2H), 3.72 (t, *J*= 5.2 Hz, 5H), 2.59 (s, 2H), 2.43 (s, 2H)
11		7.06-7.014 (m, 4H), 6.71 (s, 1H), 4.49 (s, 2H), 3.66 (s, 2H), 2.59 (s, 2H), 2.43 (s, 2H), 2.25 (s, 3H)
12		7.40 (d, *J*= 7.8 Hz, 2H), 7.05 (d, *J*= 8.4 Hz, 2H), 6.78 (s, 1H), 4.53 (s, 2H), 4.39 (s, 2H), 3.76 (s, 2H), 2.57 (t, *J*= 5.7 Hz, 2H), 2.31 (t, *J*= 7.2 Hz, 2H)
13		7.28-7.07 (m, 2H), 6.95 (t, *J*= 8.2 Hz, 2H), 6.74 (s, 1H), 4.52 (s, 2H), 3.60 (s, 2H), 2.54 (s, 2H), 2.31 (d, *J*= 7.2 Hz, 2H)
14		7.41-7.30 (m,5H), 7.14 (d, *J*= 8.4 Hz, 2H), 6.91 (d, *J*= 8.4 Hz, 2H), 6.67 (s, 1H), 5.02 (s, 2H), 4.55 (s, 2H), 3.72 (s, 2H), 2.65 (2, 4H)
15		RT : 3.82-4.54 (Mass : 306.1)

Example 16. Preparation of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid (16f)



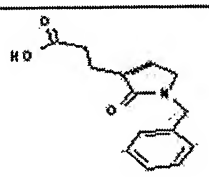
10.8 mg of $LiOH \cdot H_2O$ solution (0.25 mmol) was added to 0.86 ml of THF solution containing 55 mg of 3-[1-(2,4-dimethoxy benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.17 mmol) in a dropwise manner at 0°C. The reaction mixture was stirred for 2hrs at 0°C and 5% HCl was added to pH 1. Then the mixture was extracted three times with 10ml of ethyl acetate, the organic layer was washed with 15 ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 41 mg of 3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid (16f) (yield : 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.11 (d, J= 9.0 Hz, 1H), 6.65 (br t, 1H), 6.41 (ab, J= 6.5 Hz,1.1 Hz, 2H), 4.57 (s, 2H), 3.81-3.76 (m, 8H), 2.63 (s, 4H)

Example 17. Preparation of 3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid (17f)

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid (17f) was prepared by the similar procedure described in above Example 16 (*See* Table 2).

[Table 2]

Example	Chemical structure	NMR spectrum data
17		7.33-7.19 (m, 5H), 6.69 (br t, 1H), 4.62 (s, 2H), 3.74 (s, 2H), 2.66 (s, 4H)

Example 18. Preparation of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (18j)

Step 1. Preparation of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h)

90 mg of 3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.3 mmol) was dissolved in methanol solution at room temperature. And then 290 mg of Zn (4.44 mmol) and 0.02ml of acetic acid (0.3 mmol) were added thereto and the mixture was stirred for 48 hrs at room temperature. The resulting compound was purified by Silica gel column chromatography with ethylacetate as an eluant to give 20 mg of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h) (yield : 25%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.01 (d, *J*= 8.4 Hz, 2H), 6.62 (d, *J*= 1.8Hz, 2H), 6.60 (br t, 1H) 4.48 (s, 2H), 3.68 (d, *J*= 1.2 Hz, 3H), 3.65 (s, 4H), 2.66-2.58 (m, 4H)

Step 2. Preparation of 3-[1-(4-benzoylamino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (i)

10mg of 3-[1-(4-amino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (h) prepared by above Step 1 was dissolved in methylene chloride solution (0.04 mmol) at room temperature. And then 8.5 μl of benzoyl chloride (0.07 mmol) and 19.1 μl of diisopropylamine (0.11 mmol) were added thereto and the mixture was stirred for 2 hrs at 0°C. The reaction was quenched with methanol and the mixture was extracted three times with 10 ml of ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with ethyl acetate and hexane (1:2) as an eluant to give 12 mg of 3-[1-(4-benzoylamino-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (i) (yield : 87%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.88-7.83 (m, 3H), 7.62-7.47 (m, 6H), 6.68 (br t, 1H), 4.62 (S, 2H), 3.75 (d, 2H), 3.68 (s, 3H), 2.67-2.64 (m, 4H)

Step 3. Preparation of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (j)

7 mg of compound (i) prepared by the above Step 2 was dissolved in methanol solution (0.02 mmol) and then 1.7 M methanolic suspension solution containing

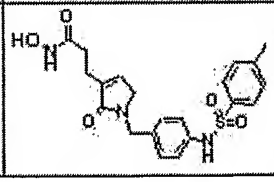
NH_2OK (0.4 ml, 0.68 mmol) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.01 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 3.2 mg of N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide (j) (yield : 46%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J*= 6.6 Hz, 2H), 7.62 (d, *J*= 8.7 Hz, 2H), 7.53-7.39 (m, 4H), 7.17(d, *J*= 8.4 Hz, 2H), 6.77 (br t, 1H), 4.57 (s, 2H), 3.77 (s, 2H), 2.58 (t, *J*= 7.3 Hz, 2H), 2.31 (t, *J*= 7.2Hz, 2H)

Example 19. Preparation of N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (19j)

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (19j) was prepared by the similar procedure described in above Example 18 (*See* Table 3).

[Table 3]

Example	Chemical structure	NMR spectrum data
19		7.61 (t, *J*= 7.0 Hz, 3H), 7.05-6.89 (m, 6H), 4.54 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H), 2.37 (s, 3H), RT : 3.87-4.34 (Mass : 430.0)

Example 20. Preparation of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide(20q)

Step 1. Preparation of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o)

587 mg of 2-methylene-succinate 4-methyl ester (4.07 mmol), 781 mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.07 mmol) and 75 mg of 4-(dimethylamino)pyridine (0.61 mmol) were added to the reaction solution containing 300 mg of allylbenzylamine (2.04 mmol) dissolved in methylene chloride solution (0.5 M) with stirring for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was diluted with ethyl acetate, washed with

10ml of solution mixture mixed with saturated $NaHCO_3$ solution and saturated NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 272 mg of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o) (yield : 49%).

^{1}H-NMR (300 MHz, CDCl3) δ 7.30-7.22 (m, 5H), 5.84-5.71 (m, 1H), 5.37-5.15 (m, 4H), 4.75-4.65 (m, 2H), 4.02 (s, 2H), 3.63 (s, 3H), 3.48 (s, 2H)

Step 2. Preparation of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p)

234 mg of 3-(allyl-benzyl-carbamoyl)-but-3-enoic acid methyl ester (o) (0.1 mmol) prepared by the above Step 1 was added to the catalyst solution containing 36 mg of Grubb's (I) catalyst (0.04 mmol) such as ruthenium dissolved in CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 180 mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p) (yield : 85%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 6.94 (t, J= 1.5 Hz, 1H), 4.61 (s, 2H), 3.79(d, J = 0.7 Hz, 2H), 3.70 (s, 3H), 3.37 (d, J = 1.5 Hz, 2H)

Step 3. Preparation of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide (q)

24 mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester (p) prepared by the above Step 2 was dissolved in methanol solution (0.1 mmol) and then 1.7 M methanolic suspension solution containing NH_2OK (0.4 ml, 0.68 mmol) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 12 mg of 2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide (q) (yield : 48%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 7.05 (br t, 1H), 4.63 (s, 2H), 3.90 (s, 2H), 3.30 (t, *J*= 1.5 Hz, 1H), 3.13 (s, 2H)

Example 21. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (21q)

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (21q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

Example 22. Preparation of N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide (22q)

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-acetamide (22q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

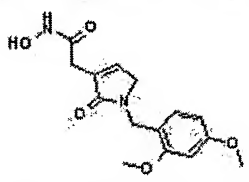
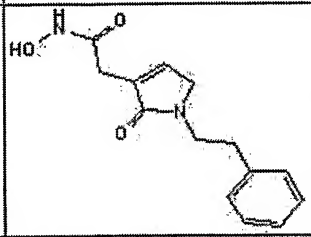
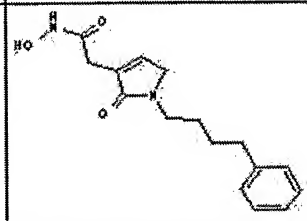
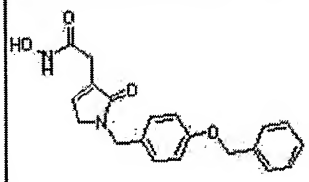
Example 23. Preparation of N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide (23q)

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-acetamide (23q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

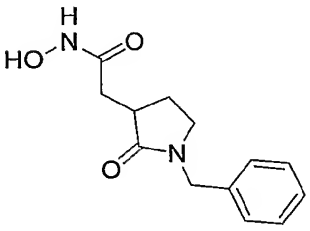
Example 24. Preparation of 2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (24q)

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide (24q) was prepared by the similar procedure described in above Example 20 (*See* Table 4).

[Table 4]

Example	Chemical structure	NMR spectrum data
21		7.12 (d, J= 8.4 Hz, 2H), 6.90(d, J= 20.7 Hz, 1H), 6.43 (d, J= 6.0 Hz), 4.57 (d, J= 2.7 Hz, 2H), 3.86 (d, J= 15.9 Hz, 2H), 3.79 (d, J= 3.0 Hz, 6H)
22		7.29-7.14 (m, 5H), 6.90 (br t, 1H), 3.75-3.65 (m, 4H), 3.23 (s, 1H), 2.92-2.84 (m, 2H)
23		7.21 (t, J= 7.4 Hz, 2H), 7.11 (d, J= 7.8 Hz,3H), 6.76 (br t, 1H), 5.22 (s, 1H), 3.30 (t, J= 3.3 Hz, 1H), 2.58 (t, J= 7.0 Hz, 2H), 2.04 (s, 3H), 1.82 (s, 3H), 1.57 (s, 4H)
24		7.39-7.31 (m, 5H), 7.13 (d, J= 8.4 Hz, 2H), 6.92 (d, J= 8.7 Hz, 3H), 5.03 (s, 2H), 4.56 (s, 2H), 3.82 (d, J= 13.8 Hz, 2H), 3.53 (s, 1H), 3.31 (s, 1H)

Example 25. Preparation of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s)



Step 1. Preparation of (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r)

30 mg of (1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-acetic acid methyl ester

was dissolved in methanol solution (0.12 mmol) under nitrogen atmosphere. Then 2.6 mg of Pd-C (0.02 mmol) was added thereto, and hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with with a solvent mixture mixed with EtOAc and hexane (1:1) as an eluant to give (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r) (yield : 95%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 4.44 (ab, *J*= 19.8 Hz, 7. 4Hz, 2H), 3.67 (s, 3H), 3.21-3.16 (m, 2H), 2.9 6(m, 2H), 2.43 (dd, *J*= 8.7 Hz, 7.9 Hz, 1H), 2.34-2.23 (m, 1H), 1.76-1.65 (m, 1H)

Step 2. Preparation of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s)

12mg of (2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetic acid methyl ester (25r) prepared by the above Step 1 was dissolved in methanol solution (0.04 mmol) and then 1.7 M methanolic suspension solution containing NH_2OK (0.07 ml, 0.12 mmol) was added thereto at 0°C and the resulting mixture was stirred for 4 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 1.6 mg of 2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide (25s) (yield : 8%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 5H), 4.46 (d, *J*= 8.1Hz, 2H), 3.35-3.20 (m, 2H), 3.01-2.71 (m, 2H), 2.66-2.44 (m, 2H), 2.35-2.22 (m, 2H), 1.81-1.58 (m, 2H)

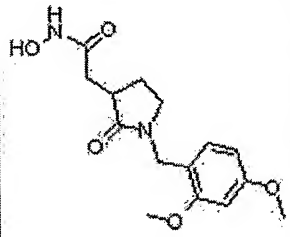
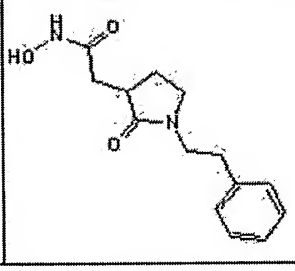
Example 26. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide (26s)

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide (26s) was prepared by the similar procedure described in above Example 25 (*See* Table 5).

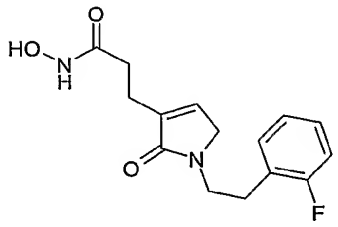
Example 27. Preparation of N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)-acetamide (27s)

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide (27s) was prepared by the similar procedure described in above Example 25 (*See* Table 5).

[Table 5]

Example	Chemical structure	NMR spectrum data
26		7.10 (t, J= 9.3 Hz, 1H), 6.44 (t, J= 2.6 Hz, 2H), 4.43 (dd, J= 14.3 Hz, 14.8 Hz, 2H), 3.78 (s,6H), 3.31-3.21 (m, 2H), 2.88-2.68 (m, 1H), 2.56-2.49 (m, 1H), 2.26-2.22 (m, 1H), 1.71-1.60 (m, 1H)
27		7.30-7.15 (m, 5H), 3.50(t, J= 7.1 Hz, 2H), 3.25-3.11 (m,2H), 2.86-2.66 (m, 3H), 2.57-2.44 (m, 1H), 2.32-2.21 (m, 2H), 1.77-1.62 (m, 1H)

Example 28. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y)



Step 1. Preparation of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u)

1.02 g of *p*-toluensulfonyl chloride (5.35 mM), 1.24 ml of diisopropyl ethylamine (7.13 mmol) and 86mg of 4-(dimethylamino)pyridine (0.71 mmol) were added to the reaction solution (3.57 mmol) containing 500 mg of 2-(2-fluoro-phenyl)-ethanol (3.57 mmol) dissolved in methylene chloride solution with stirring for 6 hrs at 0 °C under Ar atmosphere, and then the reaction mixture was stirred for 12hrs at room temperature. The resulting mixture was neutralized with ammonium chloride, extracted with ethyl acetate and washed with saturated NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:7) as an

eluant to give 740 mg of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u) (yield : 70%).

Step 2. Preparation of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v)

0.89ml of allylamine (11.9 mmol) and 0.31ml of diisopropyl ethylamine (1.78mM) were added to the reaction solution (1.2 mmol) containing 350 mg of toluen-4-sulfonate-2-(2-fluoro-phenyl)-ethyl ester (u) prepared by above Step 1 dissolved in acetonitrile solution with stirring for 6 hrs at 80 °C. After the reaction mixture was neutralized with 10% NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 141 mg of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v) (yield : 66%).

Step 3. Preparation of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w)

106 mg of 2-methylene-pentane dionate-5-methyl ester (0.67 mmol), 139 mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (0.73 mmol) and 20 mg of 4-(dimethylamino)pyridine (0.17 mmol) were added to reaction solution (0.56 mmol) dissolving 100 mg of allyl-[2-(2-fluoro-phenyl)-ethyl]-amine (v) prepared by above step 2 in methylene chloride and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with 10ml of saturated $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 128 mg of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w) (yield : 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.09 (m, 1H), 7.04-6.94 (m, 3H), 5.84 -5.57 (m, 1H), 5.13 (t, *J*= 10.7 Hz, 4H), 5.06-4.94 (m, 2H), 3.79 (s, 2H), 3.62 (s, 4H), 3.53 (d, *J*= 5.4 Hz, 3H), 2.89 (d, *J*= 6.0 Hz, 3H)

Step 4. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x)

100 mg of 4-{allyl-[2-(3-fluoro-phenyl)-ethyl]-carbamoyl}-pent-4-enoic acid methyl ester (w) (0.31 mmol) prepared by the above Step 3 was added to the catalyst solution containing 27 mg of ruthenium catalyst (0.03 mmol) dissolved in 31.3 ml of CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 69 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x) (yield : 75%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16-7.12 (m, 2H), 7.03-6.93 (m, 2H), 6.59 (br t, 1H), 3.67 -3.65 (m, 4H), 3.62 (s, 3H), 2.89 (t, *J*= 7.3 Hz, 2H), 2.56 (s, 4H)

Step 5. Preparation of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y)

38 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionic acid methyl ester (x) prepared by the above Step 4 was dissolved in methanol solution (0.13 mmol) and then 1.7 M methanolic suspension solution containing NH_2OK (0.38 ml, 0.65 mmol) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 25 mg of 3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (28y) (yield : 65%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.08 (m, 2H), 7.02-6.92 (m, 2H), 6.69 (br t, 1H), 3.69 (s, 2H), 3.63 (t, *J*= 7.0 Hz, 2H), 2.87 (t, *J*= 7.0 Hz, 2H), 2.51 (t, *J*= 7.0 Hz, 2H), 2.25 (t, *J*= 7.3 Hz, 2H)

Example 29. Preparation of 3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (29y)

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (29y) was prepared by the similar procedure described in above Example 28 (*See* Table 6a).

Example 30. Preparation of 3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (30y)

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (30y) was prepared by the similar procedure described in above Example 28 (*See* Table 6a).

Example 31. Preparation of N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (31y)

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (31y) was prepared by the similar procedure described in above Example 28 (*See* Table 6a).

Example 32. Preparation of N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (32y)

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (32y) was prepared by the similar procedure described in above Example 28 (*See* Table 6a).

Example 33. Preparation of N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (33y)

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (33y) was prepared by the similar procedure described in above Example 28 (*See* Table 6a).

Example 34. Preparation of 3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (34y)

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (34y) was prepared by the similar procedure described in above Example 28 (*See* Table 6a).

Example 35. Preparation of 3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (35y)

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide (35y) was prepared by the similar procedure described in above Example 28 (*See* Table 6b).

Example 36. Preparation of N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (36y)

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (36y) was prepared by the similar procedure described in above Example 28 (*See* Table 6b).

Example 37. Preparation of N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (37y)

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (37y) was prepared by the similar procedure described in above Example 28 (*See* Table 6b).

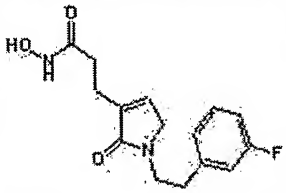
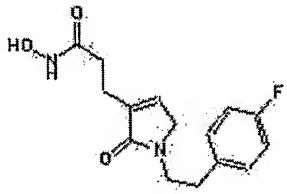
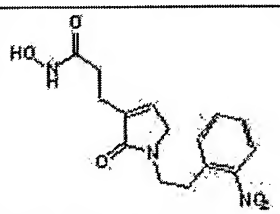
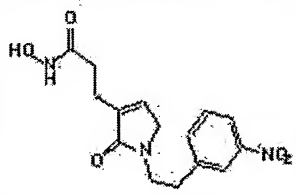
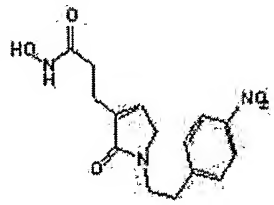
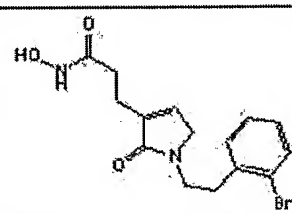
Example 38. Preparation of N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (38y)

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (38y) was prepared by the similar procedure described in above Example 28 (*See* Table 6b).

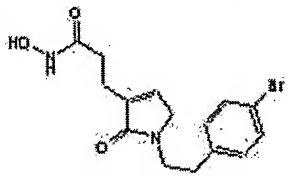
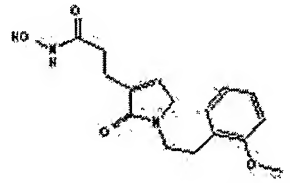
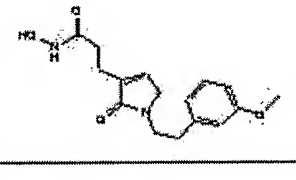
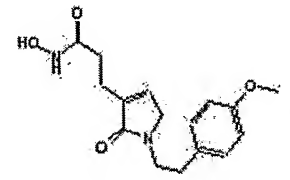
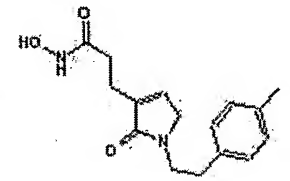
Example 39. Preparation of N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (39y)

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (39y) was prepared by the similar procedure described in above Example 28 (*See* Table 6b).

[Table 6a]

Example	Chemical structure	NMR spectrum data
29		7.25-7.18 (m, 1H), 6.90 (ab, *J*= 18.3 Hz, 4.3 Hz, 3H), 6.71 (br t, 1H), 3.65 (t, *J*= 6.9 Hz, 4H), 2.85 (t, *J*= 6.9 Hz, 2H), 2.61 (s, 2H), 2.45 (s, 2H)
30		7.11-6.94 (m, 4H), 6.70 (br t, 1H), 3.65 (s, 4H), 2.82 (s, 3H), 2.68-2.60 (m, 3H)
31		7.93 (d, *J*= 7.8 Hz, 1H), 7.56 (t, *J*= 6.7 Hz, 1H), 7.44-7.36 (m, 2H), 6.81 (br t, 1H), 3.85 (s, 2H), 3.76 (t, *J*= 7.3 Hz, 2H), 3.15 (t, *J*= 7.1 Hz, 2H), 2.54 (t, *J*= 7.1 Hz, 2H), 2.30 (t, *J*= 7.4 Hz, 2H)
32		8.00 (d, *J*= 7.2 Hz, 2H), 7.49-7.38 (m, 2H), 6.70 (br t, 1H), 3.72 (s, 2H), 3.64 (t, *J*= 7.2 Hz, 2H), 2.93 (t, *J*= 7.4 Hz, 2H), 2.48 (t, *J*= 7.3 Hz, 2H), 2.22 (t, *J*= 7.7 Hz, 2H)
33		8.09 (d, *J*= 8.4 Hz, 2H), 7.36 (d, *J*= 9.6 Hz, 2H), 6.74 (br t, 1H), 3.76 (d, *J*= 1.2 Hz, 1H,), 3.69(t, *J*= 7.1Hz, 1H), 3.29 (d, *J*= 7.8 Hz, 1H), 3.26 (dd, *J*= 1.8 Hz, 1.5 Hz, 1H), 2.97 (t, *J*= 7.3 Hz, 2H), 2.49 (t, *J*= 6.9 Hz, 2H), 2.25 (t, *J*= 7.6 Hz, 2H)
34		7.48 (d, *J*= 8.1 Hz, 2H), 7.21-7.13 (m, 2H), 7.07-7.02 (m, 1H), 6.71 (br t, 1H), 3.70-3.62 (m, 4H), 2.98 (t, *J*= 7.3 Hz, 2H), 2.52 (t, *J*= 7.3 Hz, 2H), 2.27 (t, *J*= 7.6 Hz, 2H)

[Table 6b]

Example	Chemical structure	NMR spectrum data
35		7.40 (d, *J*= 8.4 Hz, 2H), 7.10 (d, *J*= 8.1 Hz, 2H), 6.79 (br t, 1H), 3.78 (d, *J*= 1.2 Hz, 2H), 3.66 (t, *J*= 7.3 Hz, 2H), 2.85 (t, *J*= 7.1 Hz, 2H), 2.54 (t, *J*= 7.1 Hz, 2H), 2.30 (t, *J*= 7.4 Hz, 2H)
36		7.19-7.13 (m, 1H), 7.03-7.01 (m, 1H), 6.81(t, *J*= 7.4 Hz, 2H), 6.70 (br t, 1H), 3.78(s, 3H), 3.69 (s, 2H), 3.63 (t, *J*= 7.0 Hz, 2H), 2.85 (t, *J*= 7.1 Hz, 2H), 2.52 (t, *J*= 7.7 Hz, 2H), 2.27 (t, *J*= 7.6 Hz, 2H)
37		7.14(t, *J*= 7.6 Hz, 1H), 6.72-6.67 (m, 4H), 3.72 (s, 3H), 3.65 (s, 2H), 3.60 (br t, 2H), 2.80 (t, *J*= 7.1 Hz, 2H), 2.51 (t, *J*= 7.3 Hz, 2H), 2.25 (t, *J*= 7.3 Hz, 2H)
38		7.02 (d, *J*= 8.7 Hz, 2H), 6.76 (d, *J*= 8.4 Hz, 2H), 6.66 (br t, 1H), 3.72 (s, 3H), 3.62-3.56 (m, 4H), 2.76 (t, *J*= 7.3 Hz, 2H), 2.51 (t, *J*= 7.3 Hz, 2H), 2.25 (t, *J*= 7.6 Hz, 2H)
39		7.05 (s, 4H), 6.74 (br t, 1H), 3.72 (d, *J*= 1.2 Hz, 2H), 3.64 (t, *J*= 7.3 Hz, 2H), 3.31-3.29 (m, 2H), 2.82 (t, *J*= 7.3 Hz, 2H), 2.54 (t, *J*= 7.1 Hz, 2H), 2.31 (d, *J*= 7.8 Hz, 2H), 2.27 (s, 3H),

Example 40. Preparation of N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide (40ah)

Step 1. Preparation of 3-*p*-tolyl-acrylic acid methyl ester (40aa)

1.0 g of *p*-tolualdehyde (8.3 mmol) and 4.16 g of triphenyl phosphanyliden-acetic acid methyl ester (12.45 mmol) were dissolved in methylene chloride, the reaction solution was stirred at 90°C for overnight. After the resluting mixture was concentrated under reduced pressure, a solvent mixture mixed with EtOAc and hexane(1:7) was added thereto with stirring for 1hr. And then white solid was removed on filter, the residue was filtered and concentrated *in vacuo* to give 1.39 g of 3-*p*-tolyl-acrylic acid methyl ester (40aa) (yield : 95%).

Step 2. Preparation of 3-*p*-tolyl-propionic acid methyl ester (40ab)

1.39 g of 3-*p*-tolyl-acrylic acid methyl ester (40aa) prepared by above Step 1 was dissolved in methanol solution (7.9 mmol) under argon atmosphere. Then Pd-C was added thereto, hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexane (1:10) as an eluant to give 1.24 g of 3-*p*-tolyl-propionic acid methyl ester (40ab) (yield : 95%).

Step 3. Preparation of 3-*p*-tolyl-propane-1-ol (40ac)

1.24 g of 3-*p*-tolyl-propionic acid methyl ester (40ab) prepared by above Step 2 was dissolved in 100 ml of tetrahydrofuran under Argon atmosphere. Then 27 ml of lithium alluminium-hydride was added thereto with stirring for 2hrs at 0°C. After 3 ml of distilled water, 3 ml of NaOH (1N) and 9 ml of distilled water were added to the reaction mixture sequentially, the mixture was stirred for 30 min and filtered using cellite in glass filter and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:2) as an eluant to give 971 mg of 3-*p*-tolyl-propane-1-ol (40ac) (yield : 93%).

Step 4. Preparation of toluene-4-sulfonate-3-*p*-tolyl-propyl ester (40ad)

2.46 g of tosyl chloride (13 mmol), 3.4ml of diisopropylamine (19.4 mmol) and 158 mg of 4-(dimethylamino)pyridine (1.29 mmol) were added to reaction solution (6.46 mmol) dissolving 971mg of 3-*p*-tolyl-propane-1-ol (40ac) prepared by above step 3 in methylene chloride at 0°C under Ar atmosphere with stirring for 6hrs, and the reaction mixture was stirred for 12 hrs at room temperature. After the reaction mixture was neutralized with ammonium chloride, the mixture was extracted with ethyl acetate, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:7) as an eluant to give 1.3 g of toluene-4-sulfonate-3-*p*-tolyl-propyl ester (40ad) (yield : 70%).

Step 5. Preparation of allyl-(3-*p*-tolyl-propyl)-amine (40ae)

1.6 ml of allylamine (21.4 mmol) and 0.97 ml of diisopropyl ethylamine (5.5mM) were added to the reaction solution (4.27 mmol) containing 1.3 g of allyl-(3-*p*-tolyl-propyl)-amine (40ae) prepared by above Step 4 dissolved in acetonitrile solution with stirring for 6 hrs at 100 °C. After the reaction mixture was neutralized with 10%

NaOH solution, the mixture was extracted with chloroform, washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 687 mg of allyl-(3-*p*-tolyl-propyl)-amine (40ae) (yield : 85%).

Step 6. Preparation of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af)

683 mg of 2-methylene-pentane dionate-5-methyl ester (4.3 mmol), 902 mg of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (4.7 mmol) and 133 mg of 4-(dimethylamino)pyridine (1.09 mmol) were added to reaction solution (3.62 mmol) dissolving 687 mg allyl-(3-*p*-tolyl-propyl)-amine (40ae) prepared by above step 5 in 0.5 M of methylene chloride solution under Ar atmosphere and the mixture was stirred for 10 hrs at room temperature. After the resulting mixture was washed with 5% HCl solution (10 ml), the mixture was extracted with ethylacetate, washed with saturated NaCl. And then the extracts were washed with saturated 10 ml of $NaHCO_3$ solution and NaCl solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 797 mg of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af) (yield : 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.05(s, 4H), 5.70(s, 1H), 5.16-5.07(m, 4H), 3.94(s, 2H), 3.64(t, *J*=3.3Hz, 3H), 3.36(s, 2H), 2.67-2.51(m, 6H), 2.28(s, 3H), 1.83(t, *J*= 7.7Hz, 2H)

Step 7. Preparation of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag)

797 mg of 4-[allyl-(3-*p*-tolyl-propyl)-carbamoyl]-pent-4-enoic acid methyl ester (40af) (2.6 mmol) prepared by the above Step 6 was added to the catalyst solution containing 180 mg of ruthenium catalyst (0.1 mmol) dissolved in 200 ml of CH_2Cl_2 under Ar atmosphere. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:1) as an eluant to give 391 mg of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 4H), 6.56 (s, 1H), 3.67 (s, 2H), 3.55 (s, 3H), 3.37 (t, *J*= 7.2 Hz, 2H), 2.48 (t, *J*= 8.2 Hz, 6H), 2.19 (s, 3H), 1.76 (t, *J*= 7.6 Hz, 2H)

Step 8. Preparation of N-hydroxy-3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (40ah)

100 mg of 3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (40ag) prepared by the above Step 7 was dissolved in methanol solution (0.33 mmol) and then 1.7 M methanolic suspension solution containing NH_2OK (0.82 ml, 5.0 mmol) was added thereto at 0°C and the resulting mixture was stirred for 8 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:9) as an eluant to give 50 mg of N-hydroxy-3-[2-oxo-1-(3-*p*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (40ah) (yield : 50%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.21 (s, 4H), 6.95 (s, 1H), 3.96 (s, 2H), 3.60 (s, 2H), 2.72 (s, 5H), 2.45 (s, 3H), 1.99 (s, 2H)

Example 41. Preparation of N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (41ah)

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (41ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 42. Preparation of N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (42ah)

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (42ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 43. Preparation of N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (43ah)

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (43ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 44. Preparation of 3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (44ah)

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (44ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 45. Preparation of 3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (45ah)

3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (45ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 46. Preparation of N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (46ah)

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (46ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

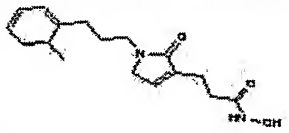
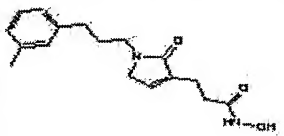
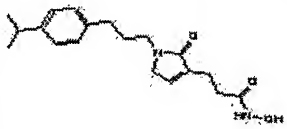
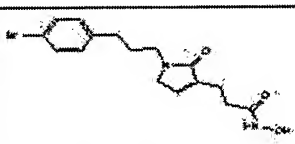
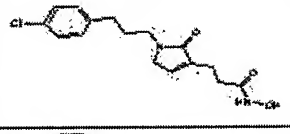
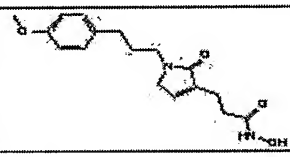
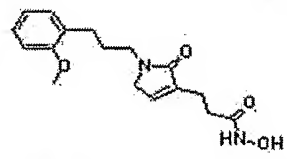
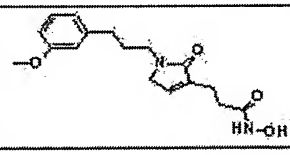
Example 47. Preparation of N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (47ah)

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (47ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

Example 48. Preparation of N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (48ah)

N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (48ah) was prepared by the similar procedure described in above Example 40 (*See* Table 7).

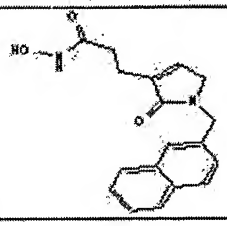
[Table 7]

Example	Chemical structure	NMR spectrum data
41		7.08 (d, J= 4.2 Hz, 4H), 6.69 (s, 1H), 3.80 (s, 2H), 3.48 (d, J= 6.6 Hz, 2H), 2.57 (d, J= 9.0 Hz, 6H), 2.25 (d, J= 6.3 Hz, 4H), 1.79 (s, 2H)
42		7.02-6.97 (m, 1H), 6.81 (d, J= 8.4 Hz, 3H), 6.64 (s, 1H), 4.07 (s, 2H), 3.71 (s, 2H), 3.32 (t, J= 7.4 Hz, 2H), 2.43 (t, J= 7.7Hz, 5H), 2.17 (t, J= 6.5 Hz, 4H), 1.78-1.68 (m, 2H)
43		10.23 (s, 1H), 7.09 (dd, J= 6.0 Hz, 4H), 6.73 (s, 1H), 3.79 (s, 2H), 3.45 (t, J= 5.1 Hz, 2H), 2.87-2.80 (m, 1H), 2.61 (s, 1H), 2.56 (t, J= 5.9 Hz, 2H), 2.46 (s, 2H), 1.88-1.81 (m, 2H), 1.26-1.19 (m, 6H)
44		7.23 (t, J= 5.5 Hz, 1H), 7.14 (t, J= 5.5 Hz, 3H), 6.73 (s, 1H), 3.77 (s, 2H), 3.43 (t, J= 5.0 Hz, 2H), 2.58 (t, J= 5.7 Hz, 4H), 2.45 (s, 2H), 1.88-1.81 (m, 2H)
45		7.23-7.04 (m, 4H), 6.73 (s, 1H), 3.77 (s, 2H), 3.43 (t, J= 5.7 Hz, 2H), 2.56 (t, J= 12.9 Hz, 3H), 2.42 (s, 2H), 1.83 (t, J= 6.7 Hz, 2H)
46		7.03 (d, J= 8.7 Hz, 2H), 6.79-6.75 (m, 2H), 6.72 (s, 1H), 3.72 (d, J= 9.9 Hz, 5H), 3.40 (t, J= 7.3 Hz, 2H), 2.58-2.42 (m, 6H), 1.78 (t, J= 7.4 Hz, 2H)
47		7.16-7.06 (m, 2H), 6.84-6.67 (m, 3H), 3.79 (t, J= 5.5 Hz, 2H), 3.75 (t, J= 3.4Hz, 3H), 3.50-3.41 (m, 2H), 2.55 (t, J= 7.7Hz, 3H), 2.43 (s, 1H), 1.87 (s, 2H), 1.84-1.77 (m, 2H)
48		7.19-7.10 (m, 1H), 6.71 (d, J= 10.8Hz, 4H), 3.75 (s, 5H), 3.49-3.40 (m, 2H), 2.55 (t, J= 7.7Hz, 4H), 2.43 (s, 2H), 1.88-1.84(m, 2H)

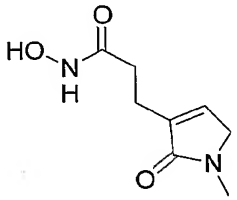
Example 49. Preparation of N-hydroxy-3-(1-naphthalene-2-ylmethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (1e')

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (1e') was prepared by the similar procedure described in above Example 1 (*See* Table 8).

[Table 8]

Example	Chemical structure	NMR spectrum or LC-MS data
49		RT :3.93-5.93 (Mass : 311.2)

Example 50. Preparation of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h')



Step 1. Preparation of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2f)

0.1 ml of triethylsilane (0.63 mmol) was added to the reaction solution containing 200 mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid methyl ester (0.63 mmol) dissolved in 0.7 ml of trifluoroacetic acid solution at 0°C. After the reaction mixture was heated for 1 hr, the mixture was filtered and concentrated *in vacuo* to remove solvent. Then the resulting mixture was dissolved in 20 ml of chloroform solution to separate into an organic layer and water layer. The organic layer was washed with 5ml of saturated $NaHCO_3$ solution and 5 ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (19:1) as an eluant to give 50 mg of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2f) (yield : 47%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (br t, 1H), 3.89 (d, J= 1.3 Hz, 2H), 3.63 (t, J= 1.9 Hz, 3H), 2.58 (s, 4H)

Step 2. Preparation of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g)

0.33 ml of NaHMDS solution (1.0 M in THF, 0.33 mmol) was added to 0.6 ml of THF solution containing 50 mg of 3-(2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic

acid methyl ester (2f) (0.30 mmol) prepared by the Step 1 in a dropwise manner at -79°C and stirred for 30 mins. After 0.3 ml of dimethyl sulfate 0.36 mmol) was added thereto, the reaction mixture was stirred for 4hrs at 0°C. Then the resulting mixture was dissolved in 2ml of saturated NH_4Cl solution and extracted with 7 ml of ethyl acetate to separate into an organic layer and water layer. The organic layer was washed with 2 ml of saturated $NaHCO_3$ solution and 2 ml of saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with EtOAc as an eluant to give 18 mg of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g) (yield : 33%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.65 (br t, 1H), 3.81 (s, 1H), 3.64 (s, 3H), 3.01 (s, 3H), 2.60 (t, 4H).

Step 3. Preparation of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h)

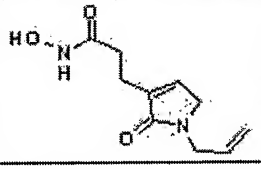
18 mg of 3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid methyl ester (2g) prepared by the above Step 2 was dissolved in methanol solution (0.1 mmol) and then 1.7 M methanolic suspension solution containing NH_2OK (0.09 ml, 0.15 mmol) was added thereto at 0°C and the resulting mixture was stirred for 1 hr at room temperature. The resulting mixture was neutralized with 0.03 ml of acetic acid, diluted with 10% methanol/chloroform solution, filtered and concentrated *in vacuo*. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and methanol (5:2) as an eluant to give 11 mg of N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide (2h) (yield : 59%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.76 (br t, 1H), 3.84 (s, 2H), 3.00 (s, 3H), 2.59 (t, J= 7.2 Hz, 2H), 2.42 (t, J= 7.2 Hz, 2H)

Example 51. Preparation of 3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (3h')

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide (3h') was prepared by the similar procedure described in above Example 50 (*See* Table 9).

[Table 9]

Example	Chemical structure	NMR spectrum data
51		6.89 (br t, 1H), 5.98-5.67 (m, 2H), 5.10-5.08 (m, 1H), 3.36 (t, J= 1.8Hz, 2H), 2.61 (s, 2H), 2.06 (s, 2H), 1.87 (s, 2H)

Example 52. Preparation of N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4n')

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (4n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

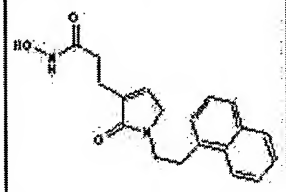
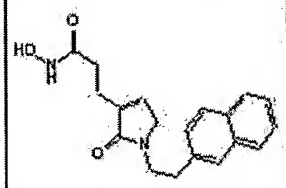
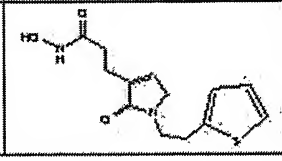
Example 53. Preparation of N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5n')

N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (5n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

Example 54. Preparation of N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6n')

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (6n') was prepared by the similar procedure described in above Example 28 (*See* Table 10).

[Table 10]

Example	Chemical structure	NMR spectrum data
52		8.01(d, *J*= 8.1 Hz, 1H), 7.77(d, *J*= 8.7 Hz, 1H), 7.66 (d, *J*= 8.1 Hz, 1H), 7.48-7.20 (m, 4H), 6.62 (br t, 1H), 3.56 (s, 2H), 3.30-3.25(m, 2H), 2.51 (t, *J*= 7.3 Hz, 2H), 2.25 (t, *J*= 7.3 Hz, 2H)
53		7.73-7.66 (m, 3H), 7.53 (s, 1H), 7.40-7.32 (m, 2H), 7.22 (s, 1H), 6.61 (br t, 1H), 3.69 (t, *J*= 7.3 Hz, 2H), 3.60 (s, 2H), 2.97 (t, *J*= 7.0 Hz, 2H), 2.49 (t, *J*= 7.2 Hz, 2H), 2.24 (t, *J*= 7.3 Hz, 2H)
54		7.08 (br t, 1H), 6.85 (t, *J*= 4.0 Hz, 1H), 6.74 (s, 1H), 6.68 (br t, 1H), 3.65 (s, 4H), 3.37-3.29 (m, 1H), 3.05 (t, *J*= 6.1 Hz, 2H), 2.51 (d, *J*= 4.8 Hz, 2H), 2.28 (s, 1H)

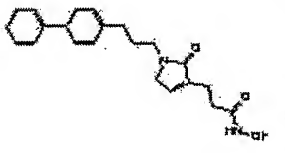
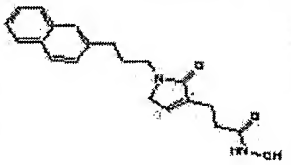
Example 55. Preparation of 3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (7w')

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide (7w') was prepared by the similar procedure described in above Example 40 (*See* Table 11).

Example 56. Preparation of N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8w')

N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide (8w') was prepared by the similar procedure described in above Example 40 (*See* Table 11).

[Table 11]

Example	Chemical structure	NMR spectrum data
55		7.51 (dd, *J*= 8.0 Hz, 4H), 7.37 (t, *J*= 7.4 Hz, 2H), 7.26 (q, *J*= 7.2 Hz, 3H), 6.81 (s, 1H), 4.79 (s, 2H), 3.89 (s, 2H), 3.48 (t, *J*= 7.1 Hz, 2H), 2.64 (t, *J*= 7.7 Hz, 2H), 2.56 (t, *J*= 5.1 Hz, 2H), 2.32 (t, *J*= 6.9 Hz, 1H)
56		10.54 (s, 1H), 7.71 (dd, *J*= 7.9 Hz, 3H), 7.54 (s, 1H), 7.41-7.33 (m, 2H), 7.24(d, *J*= 7.8 Hz, 1H), 6.64 (s, 1H), 3.67 (s, 2H), 3.40 (s, 2H), 2.69 (t, *J*= 6.7 Hz, 2H), 2.57 (s, 2H), 2.41 (s, 2H), 1.86 (s, 2H)

Example 57. Preparation of 3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydropyridin-3-yl]N-hydroxypropionamide(e1)

Step 1. Preparation of But-3-enyl-(2,4-dimethoxybenzyl)amine (b)

0.5 ml of 1-Bromo-3-butene (4.93 mmol) and 0.94 ml of diisopropyl ethylamine (5.40 mmol) were added to the reaction solution containing 0.74ml of 2, 4-dimethoxybenzylamine(a) (4.93 mmol) dissolved in methylene chloride with stirring and the mixture was stirred at room temperature for overnight. The reaction mixture was washed with saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with EtOAc solvent as an eluant to give 436mg of the pure title compound (b) (yield: 40%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.10(d, *J*= 8.1 Hz, 1H), 6.41(m, 2H), 5.75(m, 1H), 5.01(m, 2H), 3.78(s, 3H), 3.77(s, 3H), 3.70(s, 2H), 2.63(t, *J*=7.5 Hz, 2H), 2.24(m, 2H)

Step 2. Preparation of 4-[But-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c)

714 mg of 2-methylene-pentane dionate-5-methyl ester (4.52 mmol), 953 mg of EDC (4.97 mmol) and 110mg of DMAP (0.9 mmol) were added to 0.5 M of reaction solution dissolving the compound (b) prepared by above step 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature. The resulting mixture was diluted with ethyl acetate, and washed with 5% HCl solution (10 ml) and 10 ml of

saturated $NaHCO_3$ solution to separate into an organic layer and water layer. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with EtOAc and hexanes (1:2) as an eluant to give 1.39 g of 4-[but-3-enyl-(2,4-dimethoxybenzyl)-carbamoyl]-pent-4-enoic acid methyl ester (c) (yield : 40%).

Step 3. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d)

130 mg of the compound (c) (0.360 mmol) prepared by the above Step 2 was added to the catalyst solution containing 20 mg of ruthenium (0.024 mmol) dissolved in CH_2Cl_2. Then the mixture was stirred for 24 hrs at room temperature, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 108 mg of the title compound (d) (yield : 90%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17(d, *J*= 8.9Hz, 1H), 6.41(m, 2H), 6.26(t, *J*=4.3 Hz, 1H), 4.53(s, 2H), 3.77(s, 3H), 3.76(s, 3H), 3.62(s, 3H), 3.28(t, *J*= 7.1 Hz, 2H), 2.61-2.47(m, 4H), 2.22(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 164.8, 160.2, 158.5, 134.2, 133.9, 130.4, 118.0, 104.1, 98.3, 55.2, 51.3, 45.0, 44.3, 33.3, 26.6, 23.9

Step 4. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-propionamide (e1)

46 mg of compound (d) prepared by the above Step 3 was dissolved in methanol solution (0.138 mmol) and then 1,7 M methanolic suspension solution containing NH_2OK (0.122 ml, 0.207 mmol) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 32 mg of the title compound (e1) (yield: 73%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.122(d, *J*= 9.0 Hz, 1H), 6.415-6.331 (m, 3H), 4.505 (s, 2H), 3.750 (s, 3H), 3.744 (s, 3H), 3.271 (t, *J*= 6.9 Hz, 2H), 2.552 (m, 2H), 2.381 (m, 2H), 2.220 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 165.4, 160.2, 158.5, 135.8, 133.5, 130.4, 117.5,

104.2, 98.3, 55.3, 44.9, 44.6, 32.8, 27.1, 23.8

Example 58. Preparation of N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (e2)

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (e2) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

Example 59. Preparation of N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e3)

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e3) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

Example 60. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide (e4)

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide (e4) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

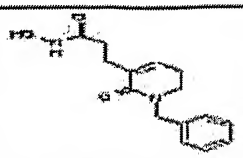
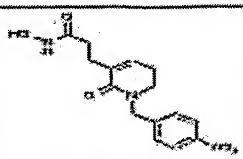
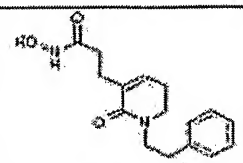
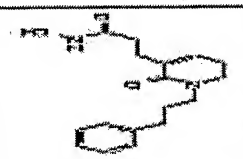
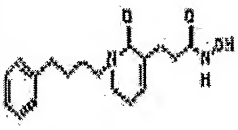
Example 61. Preparation of N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (e5)

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (e5) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

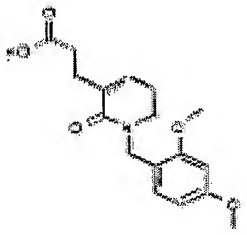
Example 62. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e6)

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (e6) was prepared by the similar procedure described in above Example 57 (*See* Table 12).

[Table 12]

Example	Chemical structure	NMR spectrum data
58		7.28(m, 5H), 6.44(t, J=4.3 Hz, 1H), 4.61(s, 2H), 3.33(m, 2H), 2.57(t, J=7.5 Hz, 2H), 2.28(m, 4H)
59		8.14(d J=8.4Hz 2H), 7.40(t J=7.2Hz 2H), 6.42(br t 1H), 4.67(s 2H), 3.32(t J=6.3Hz 2H), 2.67-2.32(m 6H)
60		7.29-7.18(m 5H) 6.40(br t 1H), 3.62(t J=7.2Hz 2H), 3.19(t J=7.1Hz 2H), 2.85(t J=7.1Hz 2H), 2.54-2.44(m 2H), 2.18-2.15(m 4H)
61		7.24-7.11(m, 5H), 6.31(br t, 1H), 3.35(br t, 2H), 3.23(br t, 2H), 2.55(d, J=6.6Hz, 4H), 2.33(s, 2H), 2.18(s, 2H), 1.80(br t, 2H)
62		7.28-7.13(m, 5H), 6.36(t, J=3.9, 1H), 3.39(t, J=6.75, 2H), 3.29(t, J=7.05, 2H), 2.62(t, J=7.05, 2H), 2.54(t, J=6.75, 2H) 2.40(t, J=6.75, 2H), 2.27(ab, J=6.0, 5.4, 2H), 1.58(t, J=2.7, 4H)

Example 63. Preparation of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (f1)



11 mg of $LiOH \cdot H_2O$ solution (0.26 mmol) was added to 0.75 ml of THF solution containing 58 mg of 3-[1-(2,4-dimethoxy benzyl)-2-oxo-1,2,5,6-tetrahydro pyridine-3-yl]-propionic acid methyl ester (d) (0.17 mmol) in a dropwise manner at 0°C. After the reaction mixture was stirred for 2hrs at 0°C and for 1hr at room temperature, 5% HCl was added to the mixture to pH 2. Then the mixture was extracted three times

with 10ml of ethyl acetate, the organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with methanol/chloroform (1:10) solvent mixture as an eluant to give 44 mg of the title compound (f1) (yield : 80%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.16(d, *J*= 8.9 Hz, 1H), 6.42(m, 2H), 6.29(t, *J*= 4.3 Hz, 1H), 4.54(s, 2H), 3.76(s, 3H), 3.76(s, 3H), 3.29(t, *J*= 7.2 Hz, 2H), 2.56(m, 4H), 2.22(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 177.7, 165.1, 160.1, 158.5, 134.6, 133.9, 130.5, 117.7, 104.1, 98.3, 55.2, 44.9, 44.5, 33.5, 26.3, 23.8

Example 64. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f2)

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f2) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

Example 65. Preparation of 3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f3)

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f3) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

Example 66. Preparation of 3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f4)

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f4) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

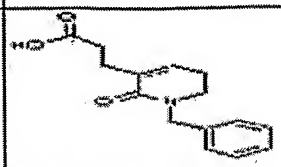
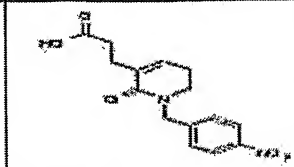
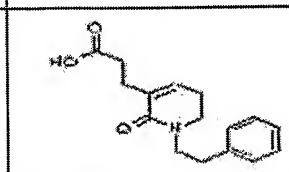
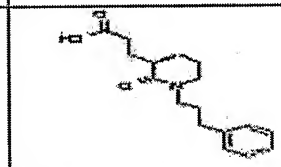
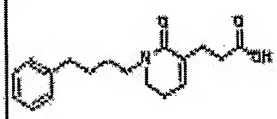
Example 67. Preparation of 3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f5)

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f5) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

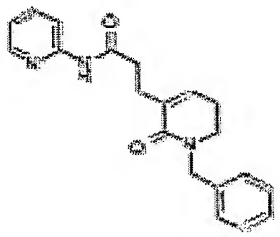
Example 68. Preparation of 3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f6)

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (f6) was prepared by the similar procedure described in above Example 63 (*See* Table 13).

[Table 13]

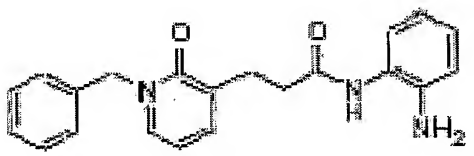
Example	Chemical structure	NMR spectrum data
64		7.25(m, 5H), 6.34(t, J=4.2Hz, 1H), 4.60(s, 2H), 3.26(t, J=7.1 Hz, 2H), 2.59(m, 4H), 2.25(m, 2H)
65		8.16(d J=8.7Hz 2H), 7.42(d, J=8.6Hz, 2H), 6.39(t J=4.3Hz, 1H) 4.69(s, 2H) 3.32(t, J=7.2Hz, 2H) 2.64-2.53(m, 4H), 2.33(dd J=6.9Hz, 5.7Hz, 2H)
66		9.92(br s 1H), 7.28-7.15(m, 5H), 6.28(t, J=4.4, 1H), 3.60(t J=7.4, 2H) 3.16(t, J=7.2, 2H) , 2.84(t, J=7.4, 2H) 2.58-2.48 (m, 4H) 2.15(AB, J=11.4, 6.8, 2H)
67		7.28-7.10(m,5H), 6.28(br, t, 1H), 5.75-5.60(m, 1H), 5.01(d, J=16.5Hz, 2H), 3.41-3.26(m, 3H) 2.63-2.26(m, 7H) 1.84(t, J=6.8Hz, 2H)
68		7.256-7.138(m, 5H), 6.33(br, t, 1H), 3.42(t, J=6.9, 2H), 3.32(t, J=7.35, 2H), 2.63(t, J=7.05, 2H), 2.547(d, J=2.4, 4H), 2.30(d, J=4.5, 2H), 1.61(q, J=1.5, 4H)

Example 69. Preparation of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide (g1)



Pyridyl amine was added to organic solvent dissolving of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (0.12 mmol) in EDC. The resulting compound was purified by Silica gel column chromatography with methanol/chloroform (1:20) solvent mixture as an eluant to give 16 mg of the title compound (g1) (yield : 39%).

Example 70. Preparation of N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g2)



40 mg of 1,2-phenylenediamine (0.37 mmol), 77 mg of EDC (0.4 mmol) and 1 mg of DMAP (3 M%) were added to reaction solution dissolving 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid prepared by above Example 8 in 1ml of methylene chloride under Argon atmosphere. After the mixture was stirred for 13 hrs at room temperature, the resulting mixture was diluted with ethyl acetate and washed with 10% NaOH solution (10 ml). Then the residue was extracted with 50 ml of chloroform, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resultant was purified by Silica gel column chromatography with a solvent mixture mixed with methanol and chloroform (1:20) as an eluant to give 96 mg of N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g2) (yield : 91%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.29 (s, 1H), 7.29-7.19 (m, 5H), 7.13 (d, 1H, *J*= 7.8Hz), 6.99-6.94 (m, 1H), 6.68 (t, 2H, *J*= 7.9Hz), 6.37 (t, 1H, *J*= 8.4Hz), 4.57 (t, 2H, *J*= 7.4Hz), 3.88 (s, 2H), 3.29-3.21 (m, 2H), 2.68 (t, 2H, *J*= 6.5Hz), 2.59 (t, 2H, 6.5Hz), 2.26-2.217 (m, 2H)

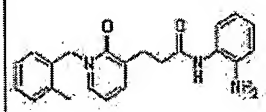
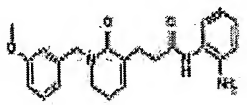
Example 71. Preparation of N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g3)

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g3) was prepared by the similar procedure described in above Example 69 and 70 (*See* Table 14).

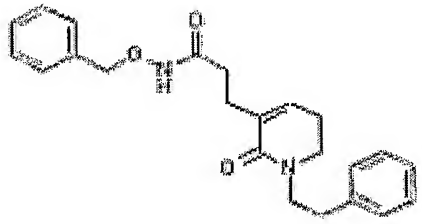
Example 72. Preparation of N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g4)

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g4) was prepared by the similar procedure described in above Example 69 and 70 (*See* Table 14).

[Table 14]

Example	Chemical structure	NMR spectrum data
71		8.23(s,1H), 7.12(dd,5H,*J*=6.6Hz), 6.979(t,1H,*J*=7.5Hz), 6.697(t,2H,*J*=8.9Hz), 6.408(t,1H,*J*=7.4Hz), 4.602(s,2H), 3.874(s,2H), 3.239(t,2H,*J*=7.1Hz), 2.702(t,2H,*J*=6.8Hz), 2.604(t,2H,*J*=6.3Hz), 2.260(t,5H,*J*=6.3Hz)
72		8.305(s,1H), 7.189-7.091(m,2H), 6.969-6.914(m,2H), 6.794-6.741(m,3H), 6.691-6.631(m,2H), 6.355(t,1H,*J*=4.1Hz), 4.539(s,2H) 3.965(s,2H), 3.707(s,3H), 3.253(t,2H,*J*=7.0Hz), 2.661-2.539(m,4H), 2.22(dd,2H,*J*=7.1Hz)

Example 73. Preparation of N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (g5)



Benzyloxyamine was added to organic solvent dissolving 30 mg of 3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (0.15 mmol) prepared by above Example 12 in EDC. The resulting compound was purified by Silica gel column chromatography with ethylacetate/chloroform (1:1) solvent mixture as an eluant to give 41 mg of the title compound (g5) (yield : 75%).

^{1}H-NMR (300 MHz, CDCl3) δ7.41-7.15 (m, 1H), 6.34 (br t, 1H), 4.88 (s, 2H), 3.58 (t, *J*= 7.4Hz, 2H), 3.16 (t, *J*= 7.2Hz, 2H), 2.82 (t, *J*= 7.2Hz, 2H), 2.53 (t, *J*= 6.8 Hz, 2H), 2.26 (br s, 1H), 2.19 (dd, *J*= 11.4, 7.1Hz, 2H)

Example 18. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)

Step 1. Preparation of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-

propionic acid methyl ester (h)

50 mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d) (0.16 mmol) prepared by the Step 3 of above Example 1 was dissolved in methanol solution at room temperature. Then 154 mg of Zn (2.36 mmol) and 0.01 ml of acetic acid (0.16 mmol) were added thereto and the mixture was stirred for 20 hrs at 80°C. The resulting compound was purified by Silica gel column chromatography with a solvent mixture mixed with ethylacetate and hexane (1:1) as an eluant to give 43 mg of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h) (yield : 92%).

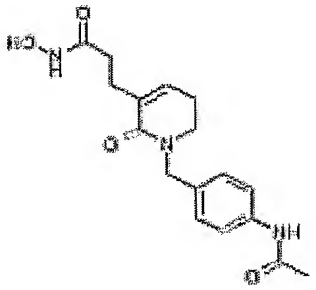
^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.22 (d, 1H, *J*= 8.5Hz), 8.11 (d, 1H, *J*= 8.4Hz), 7.37 (t, 2H, *J*= 8.3Hz), 6.33 (t, 1H, *J*= 4.3Hz), 4.66 (d, 2H, *J*= 7.5Hz), 3.63 (s, 3H), 3.29 (t, 2H, *J*= 6.6Hz), 2.63 (t, 2H, *J*= 6.9Hz), 2.54 (t, 2H, *J*= 6.6Hz), 2.28 (t, 2H, *J*= 4.2Hz)

Step 2. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (i)

17.5 mg of 3-[1-(4-amino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (h) prepared by above Step 1 was dissolved in methylene chloride solution (0.06 mmol). And then 6 μl of $(AcO)_2O$(0.07 mmol), 0.01 ml of triethylamine (0.08 mmol) and 1.0 mg of DMAP (0.008 mmol) were added thereto and the mixture was stirred for 3 hrs at 0°C. The reaction was stopped by adding methanol and the mixture was extracted three times with 10ml of ethyl acetate. The organic layer was washed with saturated NaCl solution, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with ethylacetate as an eluant to give 46 mg of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i) (yield : 44%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ8.34 (s, 1H), 7.40 (d, 2H, *J*= 8.4Hz), 7.10 (d, 2H, *J*= 8.4Hz), 6.29 (t, 1H, *J*= 4.2Hz), 4.50 (s, 2H), 3.61 (s, 3H), 3.22 (t, 2H, *J*= 7.1Hz), 2.59 (t, 2H, *J*= 7.1Hz), 2.51 (d, 2H, *J*= 6.6Hz), 2.22 (dd, 2H, *J*= 6.9Hz), 2.09 (s, 3H)

Step 3. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)



3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i) prepared by above Step 2 dissolved in organic solvent such as methanol was reacted with amine salt to give 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-propionamide (j1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d *J*= 8.0Hz 2H), 7.23 (d *J*= 8.0Hz 2H), 6.44 (br t 1H), 4.57 (S 2H), 3.33 (t, *J*= 6.5Hz, 6H) 2.57 (br t, 2H) 2.30-2.26 (m, 4H) 2.10 (s, 2H)

Example 75. Preparation of N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide (j2)

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide (j2) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

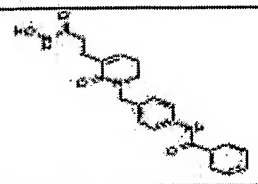
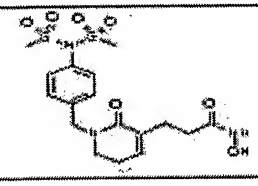
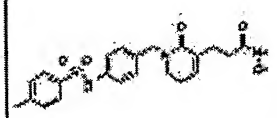
Example 76. Preparation of N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j3)

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j3) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

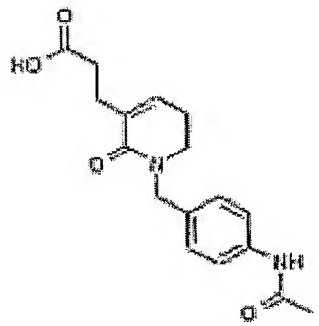
Example 77. Preparation of N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j4)

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide (j4) was prepared by the similar procedure described in above Example 74 (*See* Table 15).

[Table 15]

Example	Chemical structure	NMR spectrum data
75		7.90 (t J=7.05Hz 2H), 7.67 (d, J=8.10Hz, 2H) 7.59-7.47(m, 3H) 7.30 (d J=8.10Hz 2H), 6.45 (br t, 1H) 4.61 (s,2H) 3.36 (t, J=7.2, 2H) 3.30 (q, J=1.5Hz, 4H) 2.58 (br t,2H)
76		7.24 (q, J=8.6Hz, 4H) 6.45 (br t, 1H) 4.58 (s,2 H) 3.38-3.29 (m,7H) 2.93 (s, 3H) 2.57 (t, 2H, J=7.1) 2.34-2.24(m, 4H)
77		7.78 (d, J=8.0Hz, 2H), 7.31 (d, J=7.5Hz,2H) 7.27-7.21 (m, 4H) 6.97 (t,J=7.2Hz,1H) 4.61(d, J=3.5Hz, 1H) 3.47(s, 4H) 3.3 6-3.30 (m,1H) 2.71-.264(m, 1H) 2.51-2.44 (m,3H), 2.32 (d, J=4.5Hz, 1H)

Example 78. Preparation of 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k)



3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (i) prepared by above Step 2 of Example 18 dissolved in organic solvent such as tetrahydrofurane was reacted with LiOH to give 3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.50 (d *J*= 8.0Hz 2H), 7.23 (d *J*= 8.6Hz 2H), 6.45 (t *J*= 4.5Hz 1H), 4.58 (S 2H), 3.32 (t, *J*= 7.5Hz,3H) 2.57 (t, *J*= 7.5Hz, 2H) 2.46 (t, *J*= 7.5Hz, 2H)

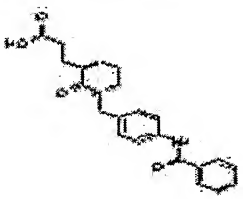
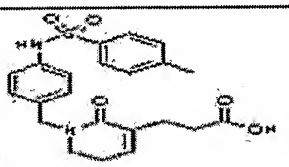
Example 79. Preparation of 3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k2)

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k2) was prepared by the similar procedure described in above Example 78 (*See* Table 16).

Example 80. Preparation of 3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k3)

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid (k3)was prepared by the similar procedure described in above Example 78 (*See* Table 16).

[Table 16]

Example	Chemical structure	NMR spectrum data
79		7.83 (d, *J*=6.9Hz, 2H), 7.59(d, *J*=8.4Hz, 2H), 7.49-7.37 (m, 4H), 7.19 (d, *J*=8.4Hz, 2H), 6.33 (q, *J*=4.5Hz, 1H) 3.26 (t, *J*=7.2Hz, 3H) 2.54-2.40 (m, 4H) 2.24 (ab, *J*=11.6Hz, 3.5Hz. 2H)
80		7.74(d, J=8.1Hz, 4H), 7.18 (d, *J*=7.8Hz,2H), 6.93 (d, *J*=8.1, 2H), 4.53(s, 2H), 3.20(br t,2H), 2.40 (s, 9H)

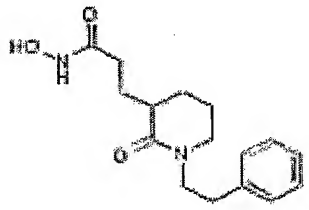
Example 81. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m)

Step 1. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l)

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in alcohol solvent under nitrogen atmosphere. Then Pd-C was added thereto, and the mixture was hydrogenated under a hydrogen balloon for 1 to 2 hrs at room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography with a solvent mixture mixed with EtOAc/hexane (1:1) as an eluant to give [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l) (yield : 74%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13 (d, 1H, *J*= 8.4Hz), 6.42 (d, 2H, *J*= 7.2Hz), 4.51(ab, 2H, *J*= 32.9, 7.4Hz), 3.76 (s, 6H), 3.66(s, 3H), 3.24-3.18(m, 2H), 2.93-2.72(m, 2H), 2.56-2.43(m, 1H), 1.98-1.55(m, 4H)

Step 2. Preparation of N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m)



[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (l) prepared by above Step 1 was reacted with amine salt to give N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide (m).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26-7.17 (m 5H), 3.61-3.44 (m 2H) 3.08-2.83 (m 4H), 2.56-2.16 (m 4H)

Example 82. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1)

Step 1. Preparation of 3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n)

2-Methylene-pentane dionate-5-methyl ester, EDC and DMAP were added to reaction solution dissolving the but-3-enyl-(2,4-dimethoxybenzyl)amine (b) prepared by above Step 1 of Example 1 in methylene chloride and the mixture was stirred for 5 hrs at room temperature to give 3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.30-7.19 (m, 5H), 5.69(br t, 1H), 5.23(s, 2H), 5.00(t, 2H, *J*= 12.6Hz), 4.74(s, 2H), 3.61(s, 3H), 3.42(s, 4H), 2.30(q, 2H, *J*= 7.2Hz)

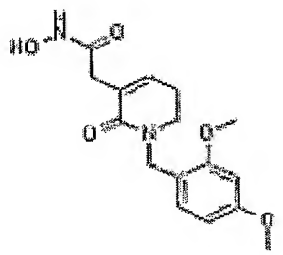
Step 2. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-

yl]-acetic acid methyl ester (o)

3-(benzyl-but-3-enyl-carbamoyl)-but-3-enoic acid methyl ester (n) prepared by above Step 1 was added to the catalyst solution containing Grubb's (I) catalysis such as ruthenium dissolved in organic solvent such as CH_2Cl_2 to give [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.17 (d, 1H, *J*= 6.2Hz), 6.42-6.36 (m, 3H), 4.54 (s, 2H), 3.76 (d, 6H, *J*= 3.0Hz), 3.66 (s, 3H), 3.35(t, 2H, *J*=6.9Hz), 3.28(s, 2H), 2.29(ab, 2H, *J*= 11.3, 3.4Hz)

Step 3. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o) prepared by above Step 2 dissolved in alcohol solvent was reacted with amine salt to give 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J*=8.7Hz, 1H), 6.54(br t, 1H) 6.44 (d, *J*= 6.0Hz, 2H), 4.55 (s, 2H), 3.78(s, 6H), 3.41-3.32(m, 2H), 3.20(s, 2H), 2.0 (d, *J*=4 .5Hz, 2H)

Example 83. Preparation of 2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p2)

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p2) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

Example 84. Preparation of N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p3)

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide (p3) was prepared by the similar procedure described in above

Example 82 (*See* Table 17).

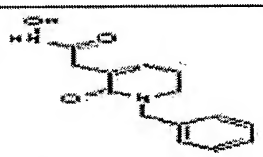
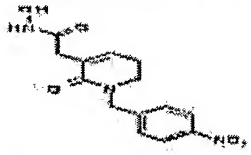
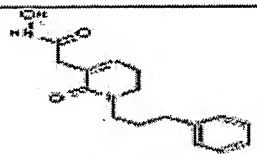
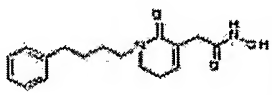
Example 85. Preparation of N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p4)

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p4) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

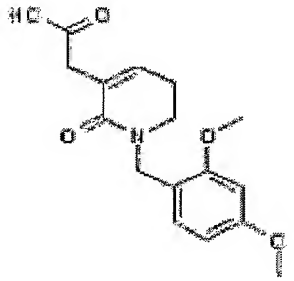
Example 86. Preparation of N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p5)

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide (p5) was prepared by the similar procedure described in above Example 82 (*See* Table 17).

[Table 17]

Example	Chemical structure	NMR spectrum data
83		7.34-7.22 (m, 5H), 6.58 (t,*J*=4.5Hz,1H) 4.60 (s, 2H) 3.39-3.30(m,3H) 3.20 (s,2H) 2.39-2.30 (m,2H)
84		8.21 (d, J=8.7Hz, 1H), 7.44 (d, *J*=8.7Hz, 2H) 6.63 (t, *J*=4.3Hz, 1H), 4.75 (s, 2H), 3.41(ab, *J*=6.5Hz, 4H), 2.43(ab, *J*=6.2Hz, 2H)
85		7.22 (d, *J*=6.5Hz, 2H) 7.14(s, 3H) 6.51(br t, 1H) 3.43-3.32 (m,5H) 3.11(s, 1H) 2.59(s,2H) 2.29(s,2H) 1.84(s,2H)
86		7.28-7.13 (m,5H), 6.54(br t, 1H), 3.44-3.31 (m,5H), 3.14(s,1H) 2.62(t,*J*=7.1Hz,2H), 2.34(s,2H), 1.58(t, *J*=3.4Hz, 4H)

Example 87. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid (q1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester (o) prepared by the Step 2 of Example 26 dissolved in TFA was reacted with LiOH to give [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid (q1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ7.18 (d, *J*= 8.7Hz, 1H), 6.54 (t, *J*= 4.3Hz, 1H), 6.45 (d, *J*= 6.6Hz, 2H), 4.60 (s,2H), 3.79(s, 6H) 3.39(t, *J*=7.3Hz, 2H), 3.34(s, 2H), 2.32(ab, *J*= 11.7Hz, 3.6Hz, 2H)

Example 88. Preparation of (1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q2)

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q2) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

Example 89. Preparation of (2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q3)

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q3) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

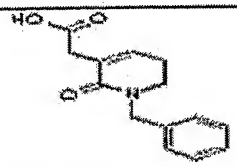
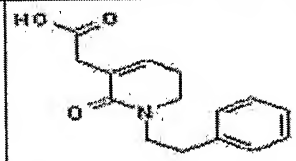
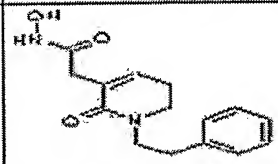
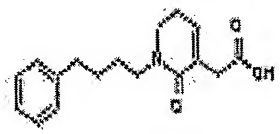
Example 90. Preparation of [2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q4)

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q4) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

Example 91. Preparation of [2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q5)

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid (q5) was prepared by the similar procedure described in above Example 87 (*See* Table 18).

[Table 18]

Example	Chemical structure	NMR spectrum data
88		7.29-7.18 (m 5H) 6.50 (t, *J*=4.5Hz, 1H), 4.58 (s, 2H), 3.31 (d *J*=7.2Hz 4H), 2.29 (ab, *J*=11.0Hz, 3.5Hz, 2H)
89		7.31-7.18 (m,5H), 6.53 (t, *J*=4.5Hz, 1H), 3.67 (t, *J*=7.2Hz, 2H), 3.30 (s, 2H), 3.23(t,*J*=7.2Hz, 2H) 2.90 (t, *J*=7.2Hz) 2.23 (ab, *J*=11.7Hz,3.6Hz, 2H)
90		7.32-7.12 (m,5H) 6.47(br t, 1H) 3.56(t, *J*=10.8Hz, 2H), 3.11 (s,4H) 2.78(d, *J*=6.0Hz, 2H) 2.14(d, *J*=10.8Hz, 2H)
91		7.29-7.14 (m,5H), 6.55(t, *J*=4.2Hz, 1H), 3.46(t, *J*=6.7Hz, 2H), 3.38(t, *J*=7.3Hz, 2H), 3.31 (s, 2H) 2.64(t, *J*=7.1Hz, 2H) 2.37(ab, *J*=6.3Hz, 2H) 1.67-1.58(m,4H)

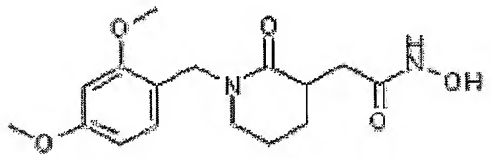
Example 92. Preparation of 2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1)

Step 1. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r)

26 mg of [1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid methyl ester(o) (0.08 mmol) was dissolved in methanol solution under Ar atmosphere. 1.7 mg of 10% Pd-C was added thereto and the mixture was hydrogenated under a hydrogen balloon. The reaction mixture was stirred for 5 hrs at room temperature, filtered and concentrated *in vacuo*. The resulting compound was purified with Silica gel column chromatography to give 25 mg of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r) (yield : 99%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J*= 8.4 Hz, 2H), 6.41 (dd, *J*= 8.4 Hz, 2H), 6.41 (s, 1H), 4.51 (dd, *J*= 32.7, 14.9 Hz, 2H), 3.76 (s, 6H), 3.66 (s, 3H), 3.22 (dd, *J*= 7.5, 4.6Hz, 2H), 2.90 (dd, *J*=15.9, 5.1 Hz, 1H), 2.76 (m, 1H), 2.52 (dd, *J*= 16.2, 7.5Hz, 2H), 1.98-1.55 (m, 4H)

Step 2. Preparation of [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1)



[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-acetic acid methyl ester (r) prepared by the Step 1 was reacted with amine salt to give [1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide (s1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.15(d, *J*= 9.0Hz, 1H), 6.46(t, *J*= 4.65Hz, 2H), 4.56 (q, *J*= 7.2, 23.7Hz, 2H), 3.79(s, 6H), 3.31-3.19(m, 2H), 2.86-2.69(m, 2H), 2.41(d, J=14.1Hz, 1H), 1.89-1.79 (m, 2H)

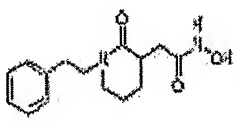
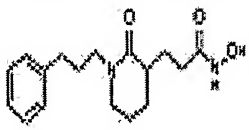
Example 93. Preparation of (2-oxo-1-phenethyl-piperidine-3-yl)-N-hydroxy-acetamide (s2)

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid (s2) was prepared by the similar procedure described in above Example 92 (*See* Table 19).

Example 94. Preparation of [2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-N-hydroxy-acetamide (s3)

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid (s3) was prepared by the similar procedure described in above Example 92 (*See* Table 19).

[Table 19]

Example	Chemical structure	NMR spectrum data
93		7.315-7.169(m,5H), 3.60(t,*J*=7.35,1H), 3.15(dd,*J*=4.8,11.1,1H), 2.917-2.856(m,1H), 2.728-2.659(m,1H), 1.698-1.426(m,4H), 1.23(d,*J*=7.05,5H)
94		7.29-7.12(m,5H) 3.47-3.35(m,2H) 3.29-3.23(m,2H)2.63-2.45(m,4H) 2.03-1.80(m,4H) 1.59-.147(m,2H), 1.33-1.19(m,3H)

Example 95. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1)

Step 1. Preparation of 5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t)

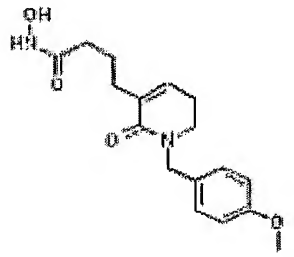
2-Methylene-pentane dionate-5-methyl ester, EDC and DMAP were added to reaction solution dissolving the but-3-enyl-(2,4-dimethoxybenzyl)amine (b) prepared by above Step 1 of Example 1 in methylene chloride solution and the mixture was stirred for 5 hrs at room temperature to give 5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t).

Step 2. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u)

5-[(4-methoxy-benzyl)-but-3-enyl-carbamoyl]-hex-5-enoic acid methyl ester (t) prepared by above Step 1 was added to the catalyst solution containing Grubb's (I) catalysis such as ruthenium dissolved in organic solvent such as CH_2Cl_2 to give 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19(d, *J*= 8.4Hz, 2H), 6.83(d, *J*= 8.4Hz, 2H), 6.25 (t, *J*= 4.2Hz, 1H), 4.54 (s, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 3.25(t, *J*= 6.9Hz, 2H) 2.33 (t, *J*= 7.3Hz, 4H), 2.24 (q, *J*= 4.5Hz, 2H), 1.80 (t, *J*= 7.2Hz, 2H) 1.56(s, 2H)

Step 3. Preparation of 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1)



4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-butyric acid methyl ester (u) prepared by Step 2 dissolved in alcohol solvent was reacted with amine salt to give 4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide (v1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.19-7.15 (m, 2H), 6.83 (d, *J*= 7.8Hz, 2H), 6.28 (br t, 1H), 4.53 (s, 2H), 3.76 (s, 3H), 3.25(dt, *J*A= 7.5Hz, *J*B= 1.8Hz, 2H), 2.38-2.23 (m, 6H), 1.85-1.76 (m, 2H)

Example 96. Preparation of 4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide (v2)

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide (v2) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

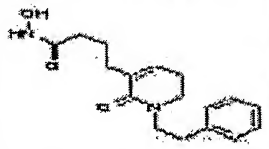
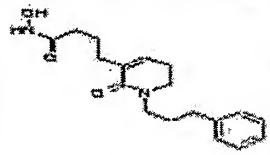
Example 97. Preparation of N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v3)

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v3) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

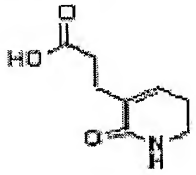
Example 98. Preparation of N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v4)

N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide (v4) was prepared by the similar procedure described in above Example 95 (*See* Table 20).

[Table 20]

Example	Chemical structure	NMR spectrum data
96		7.29-7.13(m,5H),6.24(br t,1H), 3.56 (t,J=7.56Hz 2H), 3.31-3.29 (m, 1H), 3.16 (t, J=6.9Hz, 2H), 2.80(t, J=7.2Hz, 2H), 2.14-2.03 (m, 5H), 1.66-1.61 (m, 2H)
97		7.29-7.17(m,5H), 6.32(br t,1H), 3.46 (t,J=7.3Hz 2H), 3.35 (t, J=5.9Hz, 2H), 2.63 (t, J=7.6Hz, 2H), 2.37-2.28(m, 5H), 1.99-1.73 (m, 5H)
98		7.29-7.15(m,5H), 6.31(br t,1H), 3.45 (t,J=6.5Hz 2H), 3.32 (t, J=7.1Hz, 2H), 2.64 (t, J=7.0Hz, 2H), 2.27(d, J=7.2Hz, 6H), 1.60 (s, 6H)

Example 99. Preparation of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g)

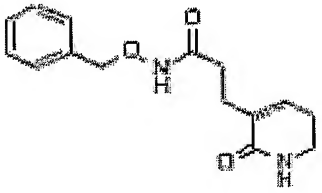


3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g) was dissolved in 0.5 ml of DMF solution. Then $BnONH_2 \cdot HCl$ (30 mg, 0.188 mmol), diisopropyl methylamine (0.033 ml, 0.189 mmol), EDC (43 mg, 0.224 mmol) and DMAP (5 mg, 0.041 mmol) were added thereto and the mixture was stirred for overnight at room temperature. The mixture was diluted with 7 ml of ethyl acetate and washed with 5% HCl (1 ml) and saturated $NaHCO_3$ solutions (1 ml). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 126 mg (yield : 55%) of the title compound (h).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28(s, br, 1H), 7.35(m, 5H), 6.45(s, br, 1H), 5.70(s, br, 1H), 4.87(s, 2H), 3.47(s, br, 2H), 2.53(m, 2H), 2.27(m, 4H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 166.9, 137.8, 135.6, 133.0, 129.1, 128.5, 78.0, 39.7, 32.8, 26.9, 24.1

Example 100. Preparation of N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (h)



29 mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid (g) was dissolved in 0.5 ml of DMF solution (0.171mM). 30 mg of $BnONH_2 \cdot HCl$ (0.188 mmol), 0.033 ml of diisopropyl methylamine (0.189 mmol), 43 mg of EDC (0.224 mmol) and 5 mg of DMAP (0.041 mmol) were added thereto and the mixture was stirred for overnight at room temperature. The mixture was diluted with 7 ml of ethyl acetate and washed with 5% HCl (1 ml) and 1ml of sat. $NaHCO_3$ solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 126 mg (yield : 55%) of the title compound (h).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.28(s, br, 1H), 7.35(m, 5H), 6.45(s, br, 1H), 5.70(s, br, 1H), 4.87(s, 2H), 3.47(s, br, 2H), 2.53(m, 2H), 2.27(m, 4H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 170.1, 166.9, 137.8, 135.6, 133.0, 129.1, 128.5, 78.0, 39.7, 32.8, 26.9, 24.1

Example 101. Preparation of 3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)

Step 1. Preparation of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (f)

310 mg of 3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester (d) (0.93 mmol) was dissolved in 3 ml of trifluoroacetic acid solution. Then 0.22 ml of triethyl silane (1.395 mmol) was added thereto and the mixture was heated for 20 min at 80°C. The solvent was removed *in vacuo* and the remaining residue was diluted in 20 ml of chloroform. The organic layer was washed with 5ml of sat. $NaHCO_3$ solution and 5ml of sat. NaCl solution. Then the organic

layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc solvent as an eluant to give 126mg (yield : 55%) of the title compound (f).

^{1}H-NMR (300 MHz, $CDCl_3$) δ6.64(s, br, 1H), 6.35(t, *J*= 3.0Hz, 1H), 3.59(s, 3H), 3.31(m, 2H), 2.48(m, 4H), 2.26(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ173.4, 166.8, 136.1, 133.5, 51.4, 39.5, 33.1, 26.0, 24.0

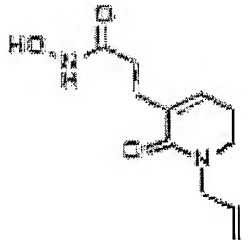
Step 2. Preparation of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i1)

0.220 ml of NaHMDS solution (1.0 M in THF, 0.22 mmol) was added to 0.5 ml of the THF solution containing 40 mg of 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (0.218 mmol) prepared by the Step 1 in a dropwise manner at -79 °C and stirred at -79 °C for 30 mins. After 0.028 ml of allyl bromide (0.327 mmol) was added to the reaction mixture, the mixture was stirred at 0 °C for 3 hrs. The reaction mixture was quenched by 2 ml of sat. NH_4Cl solution, and then the organic layer was extracted with 7ml of ethyl acetate. The combined organic layer was washed with 2ml of sat. NH_4Cl solution and 2ml of sat. NaCl solution. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc/hexane (1:2) solvent mixture as an eluant to give 36 mg (yield : 74%) of the title compound (i1).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 6.28(m, 1H), 5.74(m, 1H), 5.14(m, 2H), 3.99(d, *J*= 5.7 Hz 2H), 3.61(s, 3H), 3.27(t, *J*= 6.9 Hz, 2H), 2.51(m, 4H), 2.27(m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.6, 164.6, 134.3, 134.1, 133.3, 117.1, 51.4, 49.0, 44.6, 33.3, 26.6, 23.8

Step 3. Preparation of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide (j1)



24 mg of 3-(1-allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i1) prepared from the above Step 2 was dissolved in methanol solution (0.11 mmol) and then 0.122 ml of 1.7M NH_2OK suspension solution (0.207 mmol) was added thereto at 0°C and stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate solution, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:10) solvent mixture as an eluant to give 11 mg (yield : 48%) of the title compound (j1).

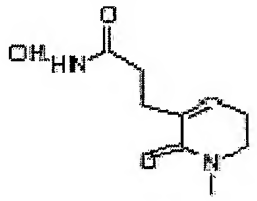
^{1}H-NMR (300 MHz, $CDCl_3$) : δ6.39(br t, 1H), 5.78-5.67(m, 1H), 5.17(d, *J*=5.4 Hz, 1H), 5.12(s, 1H), 3.98(d, *J*= 5.4 Hz, 2H), 3.30(t, *J*= 7.0 Hz, 2H), 2.54-2.28 (m, 6H)

Example 102. Preparation of N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (j2)

Step 1. Preparation of 3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (i2)

0.22 ml of 1.0 M NaHMDS solution in THF (0.22 mmol) was added to 0.5 ml of THF solution containing 80 mg 3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester (f) prepared from the step 1 in Example 3 (0.44 mmol) in a dropwise manner at -79 °C and then stirred for 30 min. After 0.48 ml of methyl bromide (0.48 mmol) was added to the reaction mixture, the solution was stirred at 0 °C for 3 hrs. The reaction mixture was quenched by 2 ml of sat. NH_4Cl solution and then the organic layer was extracted with ethyl acetate (7 ml). The combined organic layer was washed with 2ml of sat. NH_4Cl solution (2 ml) and 2 ml of sat. NaCl solution subsequently. Then the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with EtOAc solvent as an eluant to give 62 mg (yield : 72%) of the title compound (i2).

Step 2. Preparation of N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide (j2)



50 mg of 3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid methyl ester prepared from the above Step 1 was dissolved in methanol (0.25 mmol) and then 0.12 ml of 1.7M NH_2OK suspension solution in methanol (0.21 mmol) was added thereto at 0°C and the resulting mixture was stirred for 3 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid, diluted with 10 ml of ethyl acetate, filtered and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:20) solvent mixture as an eluant to give 19 mg (yield : 35%) of the title compound (j2).

^{1}H-NMR (300 MHz, CD_3OD) δ 6.15(t, *J*= 4.3 Hz, 1H), 3.41(t, *J*= 7.2Hz, 2H), 2.97(s, 3H), 2.51(t, *J*= 7.5Hz, 2H), 2.35(m, 2H), 2.22(t, *J*= 7.5Hz, 2H)

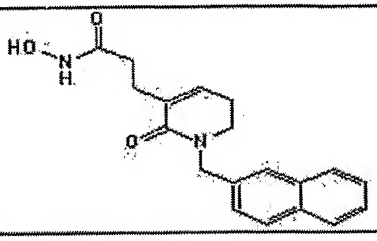
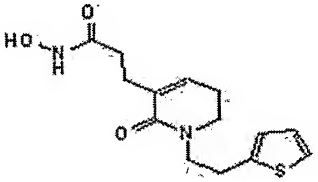
Example 103. Preparation of N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide

70 mg of 3-[1-(Naphthyl-2-yl)methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in methanol solution (0.22 mmol) and then 0.64 ml of 1.7M NH_2OK suspension in methanol (1.08 mmol) was added thereto at 0°C and the resulting mixture was stirred for 5 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid and concentrated *in vacuo*. The resulting solid was filtered with 10% methanol/chloroform solvent mixture and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:9) solvent mixture as an eluant to give 61 mg (yield : 95%) of the title compound (*See* Table 21).

Example 104. Preparation of N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide

60 mg of 3-[2-oxo-1-(2-thiophen-2-yl)ethyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid methyl ester was dissolved in methanol to be 0.20 mM solution and then 0.6 ml of 1.7M NH_2OK suspension solution in methanol (1.02 mmol) was added thereto at 0°C and the resulting mixture was stirred for 5 hrs at room temperature. The resulting mixture was neutralized with 0.02 ml of acetic acid and concentrated *in vacuo*. The resulting solid was filtered with 10% methanol/chloroform solvent mixture and concentrated *in vacuo*. The resulting compound was purified by column chromatography on Silica gel with methanol/chloroform (1:9) solvent mixture as an eluant to give 44 mg (yield : 73%) of the title compound (*See* Table 21).

[Table 21]

Example	Chemical structure	NMR spectrum data
103		8.07-7.99 (m, 1H), 7.83-7.74 (m, 2H), 7.50-7.29 (m, 4H), 6.32 (br t, 1H), 5.01 (s, 2H), 3.44(s, 2H), 3.15 (q, J=6.9 Hz, 2H), 2.71-2.54 (m,2H), 2.42 (s, 2H), 2.09 (s, 2H)
104		7.11 (d, J=4.8 Hz, 1H), 6.89 (t, J=3.9 Hz, 1H), 6.82 (s, 1H), 6.35 (br t, 1H), 3.64-3.59 (m, 2H), 3.22 (t, J=3.22 Hz, 2H), 3.09-3.04 (m, 2H), 2.54-2.50 (m, 2H), 2.35 (s, 2H), 2.20(s, 2H)

Experimental Example 1. Effect of the compound of the present invention on NO production

To test the inhibiting activity of the compounds prepared from above Examples 1 to 6 on the production of nitric oxide (NO) caused by activated macrophage by lipopolysaccharide(LPS), the amount of accumulated NO^{2-} in the cells was determined as an indicator of NO production in the medium.

Each 200 μl of RAW 264.7 cells (ATCC, USA), a mouse macrophage cell line was seeded onto each well of 96-well microtiter plate (Nunc, Sweden) to the concentration ranging from $1x10^6$ cells/ml to $5x10^6$ cells/ml, and incubated in DMEM (Dulbeco's modified eagles medium) media containing 5% FBS (fetal bovine serum) at 37°C in 5% CO_2 incubator.

Various concentrations of the compounds of the present invention ranging from 0.10.1 to 10 μM and LPS (Sigma, USA) in the final concentration of 0.3 μg/ml to activate the cell were treated to activate the cell simultaneously. The treated cells were cultured at 37°C for 24 hours in 5% CO_2 incubator and the cultured cells were collected after the cultivation.

And then, to the collected cell culture, an equal volume of Griess reagent (1% sulfanilamide, 0.1% naphthylethylenediamine dihydrochloride, and 2% phosphoric acid) was added and the culture was incubated at room temperature for 10 mins. The amount of nitrite production was determined by measuring the absorbance at 540 nm versus a $NaNO_2$ standard curve. The result was shown in Table 22 (AA: IC_{50}'s < 1, A: IC_{50}'s < 5, B: IC_{50}'s < 10, C : IC_{50}'s > 10).

As shown in Table 3, it is confirmed that compounds of the present invention showed effective NO inhibition activity.

[Table 22]

Example	TNF-alpha inhibition	Example	TNF-alpha inhibition	Example	TNF-alpha inhibition
1	B	36	-	77	B
2	A	37	-	78	A
3	A	38	-	79	A
4	AA	39	AAA	80	AA
5	A	40	AA	81	A
6	A	41	-	82	A
7	A	42	-	83	A
8	A	43	A	84	A
9	B	44	A	85	B
10	A	45	A	86	A
11	AA	46	B	87	AA
12	AA	47	-	88	AA
13	A	48	-	89	A
14	C	49	AA	90	C
15	B	50	C	91	B
16	C	51	C	92	A
17	C	52	A	93	A
18	C	53	AA	94	AA
19	B	54	A	95	A
20	C	55	A	96	A
21	C	56	AAA	97	A
22	C	57	B	98	A
23	C	58	A	99	B
24	C	59	A	100	A
25	C	60	A	101	AA
26	C	61	A	102	AA
27	C	62	AA	103	A
28	A	63	C	104	C
29	A	64	C		
30	A	65	C		
31	C	66	C		
32	C	67	C		
33	B	74	C		
34	A	75	C		
35	A	76	C		

Experimental Example 2. Effect of the compound of the present invention on TNF-alpha

To test the inhibiting activity of the compounds prepared from above Examples on the production of TNF-alpha, the concentration of TNF-alpha in the cell supernatant

was measured.

Each 200 μl of RAW 264.7 cells (ATCC, USA), a mouse macrophage cell line was seeded onto each well of 96-well microtiter plate (Nunc, Sweden) to the concentration ranging from $1x10^6$ cells/ml to $5x10^6$ cells/ml, and incubated in DMEM (Dulbeco's modified eagles medium) media containing 5% FBS (fetal bovine serum) at 37°C in 5% CO_2 incubator.

Various concentrations of the compounds of the present invention ranging from 0.10.1 to 10 μM and LPS (Sigma, USA) in the final concentration of 0.3 μg/ml were treated to activated cell simultaneously. The treated cells were cultured at 37°C for 24 hours in 5% CO_2 incubator and the cultured cells were collected after the cultivation

And then the concentration of TNF-alpha secreted from the culture supernatant of RAW 264.7 cells was determined by ELISA according to the manufacture's instruction (R&D Systems, Minneapolis, MN).

The result was shown in Table 23 (AA: IC_{50}'s < 1, A: IC_{50}'s < 5, B: IC_{50}'s < 10, C : IC_{50}'s > 10).

As shown in Table 23, it was confirmed that compounds of the present invention showed effective TNF-alpha inhibition activity.

[Table 23]

Example	TNF-alpha inhibition	Example	TNF-alpha inhibition	Example	TNF-alpha inhibition
1	B	36	-	77	B
2	A	37	-	78	A
3	A	38	-	79	A
4	AA	39	AAA	80	AA
5	A	40	AA	81	A
6	A	41	-	82	A
7	A	42	-	83	A
8	A	43	A	84	A
9	B	44	A	85	B
10	A	45	A	86	A
11	AA	46	B	87	AA
12	AA	47	-	88	AA
13	A	48	-	89	A
14	C	49	AA	90	C
15	B	50	C	91	B
16	C	51	C	92	A
17	C	52	A	93	A
18	C	53	AA	94	AA
19	B	54	A	95	A
20	C	55	A	96	A
21	C	56	AAA	97	A
22	C	57	B	98	A
23	C	58	A	99	B
24	C	59	A	100	A
25	C	60	A	101	AA
26	C	61	A	102	AA
27	C	62	AA	103	A
28	A	63	C	104	C
29	A	64	C		
30	A	65	C		
31	C	66	C		
32	C	67	C		
33	B	74	C		
34	A	75	C		
35	A	76	C		

Experimental Example 3. Toxicity test

Methods

The acute toxicity tests on ICR mice (mean body weight 25±5g) and Sprague-Dawley rats (235±10g, Jung-Ang Lab Animal Inc.) were performed using the compounds of example 80. Four group consisting of 10 mice or rats was administrated orally with 4mg/kg, 40mg/kg, 400mg/kg and 4,000mg/kg of test sample or solvents (0.2

㎖, i.p.) respectively and observed for 2 weeks.

Results

There were no treatment-related effects on mortality, clinical signs, body weight changes and gross findings in any group or either gender. These results suggested that the extract prepared in the present invention were potent and safe.

Hereinafter, the formulating methods and kinds of excipients will be described, but the present invention is not limited to them. The representative preparation examples were described as follows.

Preparation of powder

the compounds of example 80	50mg
Lactose	100mg
Talc	10mg

Powder preparation was prepared by mixing above components and filling sealed package.

Preparation of tablet

the compounds of example 80	50mg
Corn Starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and entabletting.

Preparation of capsule

the compounds of example 80	50mg
Corn starch	100mg
Lactose	100mg
Magnesium Stearate	2mg

Tablet preparation was prepared by mixing above components and filling gelatin capsule by conventional gelatin preparation method.

Preparation of injection

the compounds of example 80	50mg
Distilled water for injection	optimum amount

PH controller	optimum amount

Injection preparation was prepared by dissolving active component, controlling pH to about 7.5 and then filling all the components in 2 ㎖ ample and sterilizing by conventional injection preparation method.

Preparation of liquid

the compounds of example 80	0.1~80g
Sugar	5~10g
Citric acid	0.05~0.3%
Caramel	0.005~0.02%
Vitamin C	0.1~1%
Distilled water	79~94%
CO_2 gas	0.5~0.82%

Liquid preparation was prepared by dissolving active component, filling all the components and sterilizing by conventional liquid preparation method.

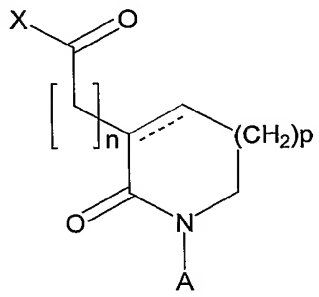
The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the present invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.

INDUSTRIAL APPLICABILITY

As described in the present invention, the 2-oxo-cyclic compound of the present invention have potent anti-inflammatory activity, therefore, it can be used as the therapeutics for treating and preventing the inflammatory disease comprising the pain or inflammation caused by rheumatic disease, for example, rheumatoid arthritis, spondyloarthopathies, gout, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, and inflammatory syndrome for example, from myositis, gingivitis, synovitis, ankylosing spondylitis, burstitis, burns and scar, inflammatory Crohn's disease, Types I diabetes.

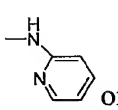
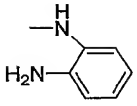
What is claimed is;

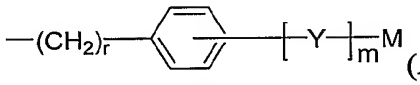
1. A novel compound represented by the following general formula (I), the pharmaceutically acceptable salt or the isomer thereof:



(I)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

A is an hydrogen, A1 group or  (A2),

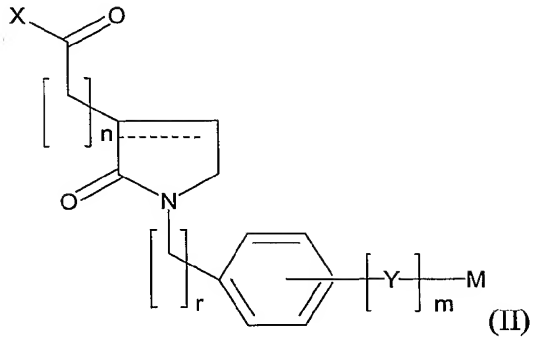
A1 is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group, wherein the Y in A2 substituted is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group, M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group, m and r is independently an integer of 1 to 5 respectively;

p is an integer of 0, 1 or 2;

n is an integer of 1 to 5;

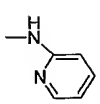
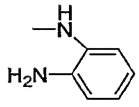
dotted line (┈) means single bond or double bond.

2. A novel compound represented by the following general formula (II), the pharmaceutically acceptable salt or the isomer thereof:



(II)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (┅) means single bond or double bond.

3. The compound according to claim 2, wherein said compound is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxypropionamide,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(3-phenyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(2-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methyl-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-

propionamide,

N-hydroxy-3-[1-(2-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(3-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[1-(4-methoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(4-bromo-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-chloro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

3-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]- N-hydroxy-propionamide,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionic acid,

3-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionic acid,

N-{4-[3-(2-hydroxycarbamoyl-ethyl)-2-oxo-2,5-dihydro-pyrrole-1-yl-methyl]-phenyl}-benzamide,

N-hydroxy-3-{2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

2-(1-benzyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-2,5-dihydro-1H-pyrrol-3-yl)- acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-2,5-dihydro-1H-pyrrol-3-yl]- acetamide,

2-[1-(4-benzyloxy-benzyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-acetamide,

2-(1-benzyl-2-oxo-pyrrolidin-3-yl)-N-hydroxy-acetamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-pyrrolidin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-(2-oxo-1-phenethyl-pyrrolidin-3-yl)- acetamide,

3-{1-[2-(2-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(3-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-fluoro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-nitro-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

3-{1-[2-(2-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

3-{1-[2-(4-bromo-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-N-hydroxy-propionamide,

N-hydroxy-3-{1-[2-(2-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(3-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-{1-[2-(4-methoxy-phenyl)-ethyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(2-*p*-tolyl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide,

N-hydroxy-3-[2-oxo-1-(3-*o*-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(3-m-tolyl-propyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(4-isopropyl-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-{1-[3-(4-bromo-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

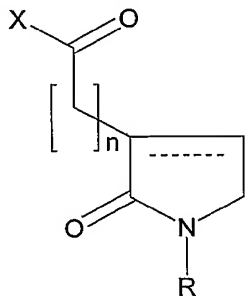
3-{1-[3-(4-chloro-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

N-hydroxy-3-{1-[3-(4-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-{1-[3-(2-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

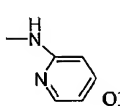
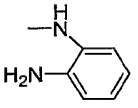
N-hydroxy-3-{1-[3-(3-methoxy-phenyl)-propyl]-2-oxo-2,5-dihydro-1H-pyrrol-3-yl}-propionamide.

4. A novel compound represented by the following general formula (III), the pharmaceutically acceptable salt or the isomer thereof:



(III)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group;

n is an integer of 1 to 5;

dotted line (┅) means single bond or double bond.

5. The compound according to claim 4, wherein said R is the group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group.

6. The compound according to claim 5, wherein said compound is one selected from the group consisting of;

N-hydroxy-3-(1-naphthalene-2-ylmethyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-propionamide,

3-(1-allyl-2-oxo-2,5-dihydro-1H-pyrrol-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-[1-(2-naphthalene-1-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

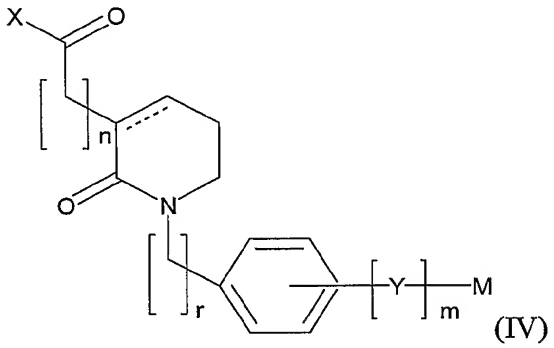
N-hydroxy-3-[1-(2-naphthalene-2-yl-ethyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-2,5-dihydro-1H-pyrrol-3-yl]-propionamide,

3-[1-(3-biphenyl-4-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-N-hydroxy-propionamide,

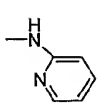
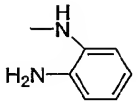
N-hydroxy-3-[1-(3-naphthalene-2-yl-propyl)-2-oxo-2,5-dihydro-1H-pyrrol-3-yl]-propionamide.

7. A novel compound represented by the following general formula (IV), the pharmaceutically acceptable salt or the isomer thereof:



(IV)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

Y is a lower alkyl group, lower alkoxy group, nitro, halogen, amine, acetamide, carbonamide or sulfonamide group;

M is a lower alkyl group or phenyl group substituted with R', of which R' is a hydrogen, lower alkyl or lower alkoxy group;

m and r is independently an integer of 1 to 5 respectively;

n is an integer of 1 to 5;

dotted line (┅) means single bond or double bond.

8. The compound according to claim 7, wherein said compound is one selected from the group consisting of;

3-[1-(2,4-Dimethoxybenzyl)-2-oxo-1,2,5,6-tetragydropyridine-3-yl]N-hydroxypropionamide,

N-hydroxy-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-hydroxy-3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy propionamide,

N-hydroxy-3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(2,4-dimethoxybenzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-pyridin-2-yl-propionamide,

N-(2-amino-phenyl)-3-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-(2-amino-phenyl)-3-[1-(2-methyl-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-benzyloxy-3-(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-4-[5-(2-hydroxycarbamoyl-ethyl)-6-oxo-3,6-dihydro-2-pyridin-1-yl-methyl]-phenyl-benzamide,

N-hydroxy-3-[1-(4-dimethylsulfonylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

N-hydroxy-3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide,

3-[1-(4-acetylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-[1-(4-benzoylamino-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

3-2-oxo-1-[4-(toluene-4-sulfonylamino)-benzyl]-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-propionic acid,

N-hydroxy-3-(2-oxo-1-phenethyl-piperidine-3-yl)-propionamide,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-

acetamide,

2-(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[1-(4-nitro-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

N-hydroxy-2-[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-acetamide,

[1-(2,4-dimethoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-acetic acid,

(1-benzyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

(2-oxo-1-phenethyl-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

[2-oxo-1-(4-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl)-acetic acid,

2-[1-(2,4-dimethoxy-benzyl)-2-oxo-piperidine-3-yl]-N-hydroxy-acetamide,

(2-oxo-1-phenethyl-piperidine-3-yl)-acetic acid,

[2-oxo-1-(3-phenyl-propyl)-piperidine-3-yl]-acetic acid,

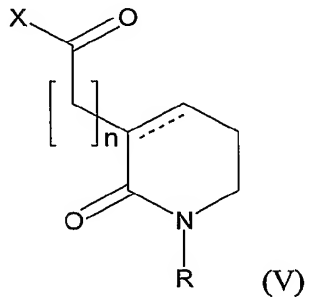
4-[1-(4-methoxy-benzyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl]-N-hydroxy-butylamide,

4-(1-phenethyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-butylamide,

N-hydroxy-4-[2-oxo-1-(3-phenyl-propyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide,

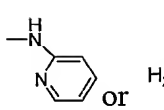
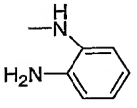
N-hydroxy-4-[2-oxo-1-(3-phenyl-butyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-butylamide.

9. A novel compound represented by the following general formula (V), the pharmaceutically acceptable salt or the isomer thereof:



(V)

wherein

X is a hydroxyl group, -NHOH, -NHOCH$_2$Ph,  or  ;

R is a lower alkyl, lower alkenyl, lower alkynyl, lower allyl group having C1 to C5 carbon atoms, a heterocyclic group or aromatic aryl group selected from thiopenyl group, naphtyl group, pyrrolyl group, furyl group and biphenyl group;

n is an integer of 1 to 5;

dotted line (═) means single bond or double bond.

10. The compound according to claim 9, wherein said compound is one selected from the group consisting of;

3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionic acid,

N-Benzyloxy-3-(2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

3-(1-Allyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-N-hydroxy-propionamide,

N-hydroxy-3-(1-methyl-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-(1-(naphthalene-2-yl-methyl)-2-oxo-1,2,5,6-tetrahydro-pyridin-3-yl)-propionamide,

N-hydroxy-3-[2-oxo-1-(2-thiophen-2-yl-ethyl)-1,2,5,6-tetrahydro-pyridin-3-yl]-propionamide.

11. A pharmaceutical composition comprising an efficient amount of the compound represented by general formula (I) to (V) or the pharmaceutically acceptable salt thereof as an active ingredient in amount effective to treat or prevent inflammatory diseases together with pharmaceutically acceptable carriers or diluents.

12. The pharmaceutical composition according to claim 11, wherein said inflammatory disease comprises the pain or inflammation caused by rheumatic disease and inflammatory syndrome.

13. The pharmaceutical composition according to claim 12, wherein said inflammatory disease comprises rheumatic disease selected from rheumatoid arthritis, spondyloarthopathies, gout, osteoarthritis, systemic lupus erythematosus and juvenile arthritis.

14. The pharmaceutical composition according to claim 12, wherein said inflammatory disease comprises the inflammatory disease selected from myositis, gingivitis, synovitis, ankylosing spondylitis, burstitis, burns and scar, inflammatory

Crohn's disease, Types I diabetes.

15. A method for preventing or treating the inflammatory disease comprising the pain or inflammation caused by rheumatic disease and inflammatory syndrome which comprises administering compound selected from the group consisting of compounds of formula (I) to (V) or pharmaceutical acceptable salts thereof in need of such prevention or treatment a therapeutically effective amount of the salt or a pharmaceutically acceptable hydrate thereof as an anti-inflammatory agent.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/001169

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 211/88

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975

Electronic data base consulted during the internationl search (name of data base and, where practicable, search terms used)
STN(Reg, CA)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Albert Padwa, et al., 'A Novel Cycloaddition Reaction of alpha-Diazo-gamma-amido Ketones Catalyzed by Rhodium(II) Acetate. Scope and Mechanistic Details of the Process', Journal of Organic Chemistry, 1996, vol.61, no. 7, pp. 2283-92 (See the right column of p.2291)	1, 7-9
X	McIntosh, J.M. et al., 'Enamines and iminium salts from amido acids', Canadian Journal of Chemistry, 1983, vol.61, no.9, pp.2016-21 (See the 16a, 16b compound, p.2017)	1, 7-9
A	US 6110930 A (Ono Pharmaceutical Co., Ltd.) 29 August 2000 (See the whole document)	1-15
A	US 6303613 B1 (AstraZeneca AB) 16 October 2001 (See the whole document)	1-15
A	US 6476023 B1 (Boehringer Ingelheim) 5 November 2002 (See the whole document)	1-15

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 AUGUST 2004 (11.08.2004)	11 AUGUST 2004 (11.08.2004)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701,
Republic of Korea
Facsimile No. 82-42-472-7140

Authorized officer
KIM, Hee Jin
Telephone No. 82-42-481-5412

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2004/001169

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 15 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compound/ composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any addition fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2004/001169

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6110930 A	29.08.00	JP 3060214 B2	10.07.00
		EP 871763 B1	12.12.01
		DE 69802858 C0	24.01.02
		AU 746048 B2	11.04.02
US 6303613 B1	16.10.01	JP 2001519805 T2	23.10.01
		EP 973772 A1	26.01.00
		AU 7091098 A1	30.10.98
		CN 1259131 T	05.07.00
US 6476023 B1	05.11.02	JP 2002539206 T2	19.11.02
		EP 1163236 A1	19.12.01
		CA 2361998 AA	21.09.00